Exhibit 93, part 4

Table 1.2 Historical trend in asbestos use per capita and status of national ban

	Use of asbestos[a] (kg per capita/year)						
Country	**1950s**	**1960s**	**1970s**	**1980s**	**1990s**	**2000s**	**National ban[b]**
Asia							
Israel	3.13	2.87	1.23	0.78	0.44	0.02	No ban
Japan	0.56	2.02	2.92	2.66	1.81	0.46	2004
Others[c] (n = 39)	0.06	0.15	0.25	0.27	0.30	0.31	3/39
Eastern Europe and Southern Europe							
Croatia	0.39	1.13	2.56	2.36	0.95	0.65	No ban
Czech Republic	1.62	2.36	2.91	2.73	1.30	0.14	2005
Hungary	0.76	1.23	2.87	3.29	1.50	0.16	2005
Poland	0.36	1.24	2.36	2.09	1.05	0.01	1997
Romania	ND	ND	1.08	0.19	0.52	0.55	2007
Spain	0.32	1.37	2.23	1.26	0.80	0.18	2002
Others[c] (n = 15)	0.79	1.57	2.35	2.05	2.35	1.72	5/15
Northern Europe and Western Europe							
Austria	1.16	3.19	3.92	2.08	0.36	0.00	1990
Denmark	3.07	4.80	4.42	1.62	0.09	NA	1986
Finland	2.16	2.26	1.89	0.78	ND	0	1992
France	1.38	2.41	2.64	1.53	0.73	0.00	1996
Germany	1.84	2.60	4.44	2.43	0.10	0.00	1993
Iceland	0.21	2.62	1.70	0.02	0	0.00	1983
Lithuania	ND	ND	ND	ND	0.54	0.06	2005
Luxembourg	4.02	5.54	5.30	3.23	1.61	0.00	2002
Netherlands	1.29	1.70	1.82	0.72	0.21	0.00	1994
Norway	1.38	2.00	1.16	0.03	0	0.00	1984
Sweden	1.85	2.30	1.44	0.11	0.04	NA	1986
United Kingdom	2.62	2.90	2.27	0.87	0.18	0.00	1999
Others[c] (n = 5)	3.05	4.32	4.05	2.40	0.93	0.05	5/5

as the Coalinga chrysotile deposits in California, USA, are reported to contain 50% or more (USGS, 2001; Virta, 2006).

1.4.2 Air

Asbestos is not volatile; however, fibres can be emitted to the atmosphere from both natural and anthropogenic sources. The weathering of asbestos-bearing rocks is the primary natural source of atmospheric asbestos. No estimates of the amounts of asbestos released to the air from natural sources are available (ATSDR, 2001). Anthropogenic activities are the predominant source of atmospheric asbestos fibres. Major anthropogenic sources include: open-pit mining operations (particularly drilling and blasting); crushing, screening, and milling of the ore; manufacturing asbestos products; use of asbestos-containing materials (such as clutches and brakes on cars and trucks); transport and disposal of wastes containing asbestos; and, demolition of buildings constructed with asbestos-containing products, such as insulation, fireproofing, ceiling and floor tiles, roof shingles, drywall, and cement (ATSDR, 2001; NTP, 2005). Concentrations of asbestos vary on a site-by-site basis and, as a result, environmental emissions are not easily estimated (ATSDR, 2001).

Table 1.2 (continued)

	Use of asbestos[a] (kg per capita/year)						
Country	**1950s**	**1960s**	**1970s**	**1980s**	**1990s**	**2000s**	**National ban[b]**
Americas, excluding South America							
Canada	2.76	3.46	4.37	2.74	1.96	0.32	No ban
Cuba	ND	ND	ND	0.15	0.36	0.74	No ban
Mexico	0.28	0.57	0.97	0.77	0.39	0.26	No ban
USA	3.82	3.32	2.40	0.77	0.08	0.01	No ban
Others[c] (n = 12)	0.06	0.22	0.44	0.29	0.07	0.07	0/12
South America							
Argentina	ND	0.88	0.76	0.40	0.18	0.04	2001
Brazil	0.27	0.38	0.99	1.25	1.07	0.74	2001
Chile	0.07	0.92	0.56	0.64	0.55	0.03	2001
Ecuador	ND	ND	0.67	0.52	0.14	0.26	No ban
Uruguay	ND	0.74	0.75	0.54	0.47	0.08	2002
Others[c] (n = 6)	0.27	0.43	0.60	0.47	0.29	0.19	0/6
Oceania							
Australia	3.24	4.84	5.11	1.82	0.09	0.03	2003
New Zealand	2.05	2.56	2.90	1.00	ND	ND	No ban
Others[c] (n = 3)	ND	ND	ND	ND	ND	0.22	0/3

[a] Numbers corresponding to use of asbestos by country and region were calculated as annual use per capita averaged over the respective decade.
[b] Year first achieved or year planned to achieve ban. When shown as fraction, the numerator is the number of countries that achieved bans and the denominator is the number of other countries in the region.
[c] Data on asbestos use were available (but mortality data unavailable) for others in each region, in which case data were aggregated.
ND, no data available; NA, not applicable because of negative use data; 0.00 when the calculated data were < 0.005; 0 if there are no data after the year the ban was introduced.
From Nishikawa et al. (2008)

1.4.3 Water

Asbestos can enter the aquatic environment from both natural and anthropogenic sources, and has been measured in both ground- and surface-water samples. Erosion of asbestos-bearing rock is the principal natural source. Anthropogenic sources include: erosion of waste piles containing asbestos, corrosion of asbestos-cement pipes, disintegration of asbestos-containing roofing materials, and, industrial wastewater run-off (ATSDR, 2001).

1.4.4 Soil

Asbestos can enter the soil and sediment through natural (e.g. weathering and erosion of asbestos-bearing rocks) and anthropogenic (e.g. disposal of asbestos-containing wastes in landfills) sources. The practice of disposing asbestos-containing materials in landfills was more common in the past, and is restricted in many countries by regulation or legislation (ATSDR, 2001).

1.4.5 Environmental releases

According to the US EPA Toxics Release Inventory, total releases of friable asbestos to the environment (includes air, water, and soil) in 1999 were 13.6 million pounds from 86 facilities that reported producing, processing, or using asbestos (ATSDR, 2001). In 2009, total releases of 8.9 million pounds of friable asbestos were reported by 38 facilities (US EPA, 2010).

1.5 Human exposure

Inhalation and ingestion are the primary routes of exposure to asbestos. Dermal contact is not considered a primary source, although it may lead to secondary exposure to fibres, via ingestion or inhalation. The degree of penetration in the lungs is determined by the fibre diameter, with thin fibres having the greatest potential for deep lung deposition (NTP, 2005).

1.5.1 Exposure of the general population

Inhalation of asbestos fibres from outdoor air, and to a lesser degree in indoor air, is the primary route of exposure for the non-smoking general population. Exposure may also occur via ingestion of drinking-water, which has been contaminated with asbestos through erosion of natural deposits, erosion of asbestos-containing waste sites, corrosion of asbestos-containing cement pipes, or filtering through asbestos-containing filters. Families of asbestos-workers may be exposed via contact with fibres carried home on hair or on clothing.

In studies of asbestos concentrations in outdoor air, chrysotile is the predominant fibre detected. Low levels of asbestos have been measured in outdoor air in rural locations (typical concentration, 10 fibres/m^3 [f/m^3]). Typical concentrations are about 10-fold higher in urban locations and about 1000 times higher in close proximity to industrial sources of exposure (e.g. asbestos mine or factory, demolition site, or improperly protected asbestos-containing waste site) (ATSDR, 2001). Asbestos fibres (mainly chrysotile) were measured in air and in settled dust samples obtained in New York City following destruction of the World Trade Center on September 11, 2001 (Landrigan *et al.*, 2004).

In indoor air (e.g. in homes, schools, and other buildings), measured concentrations of asbestos are in the range of 30–6000 f/m^3. Measured concentrations vary depending on the application in which the asbestos was used (e.g. insulation versus ceiling or floor tiles), and on the condition of the asbestos-containing materials (i.e. good condition versus deteriorated and easily friable) (ATSDR, 2001).

1.5.2 Occupational exposure

Asbestos has been in widespread commercial use for over 100 years (USGS, 2001). Globally, each year, an estimated 125 million people are occupationally exposed to asbestos (WHO, 2006). Exposure by inhalation, and to a lesser extent ingestion, occurs in the mining and milling of asbestos (or other minerals contaminated with asbestos), the manufacturing or use of products containing asbestos, construction, automotive industry, the asbestos-abatement industry (including the transport and disposal of asbestos-containing wastes).

Estimates of the number of workers potentially exposed to asbestos in the USA have been reported by the National Institute of Occupational Safety and Health (NIOSH), by the Occupational Safety and Health Administration (OSHA), and the Mine Safety and Health Administration (MSHA). OSHA estimated in 1990 that about 568000 workers in production and services industries and 114000 in construction industries may have been exposed to asbestos in the workplace (OSHA, 1990). Based on mine employment data from 2002, NIOSH estimated that 44000 miners and other mine workers may have been exposed to asbestos during the mining of asbestos and some mineral commodities in which asbestos may have been a potential contaminant (NIOSH, 2002b). More recently, OSHA has estimated that 1.3 million employees in construction and general industry face significant asbestos exposure on the job (OSHA, 2008). In addition to evidence from OSHA and MSHA that indicate a reduction in occupational exposures in the USA over the past several decades, other information compiled on workplace exposures to asbestos

indicates that the nature of occupational exposures to asbestos has changed (Rice & Heineman, 2003). Once dominated by chronic exposures in manufacturing process such as textile mills, friction-product manufacturing, and cement-pipe fabrication, current occupational exposures to asbestos primarily occur during maintenance activities or remediation of buildings that contain asbestos.

In Europe, estimates of the number of workers exposed to asbestos have been developed by CAREX (CARcinogen EXposure). Based on occupational exposure to known and suspected carcinogens collected during 1990–93, the CAREX database estimates that a total of 1.2 million workers were exposed to asbestos in 41 industries in the 15 Member States of the EU. Over 96% of these workers were employed in the following 15 industries: 'construction' (n = 574000), 'personal and household services' (n = 99000), 'other mining' (n = 85000), 'agriculture' (n = 81000), 'wholesale and retail trade and restaurants and hotels' (n = 70000), 'food manufacturing' (n = 45000), 'land transport' (n = 39000), 'manufacture of industrial chemicals' (n = 33000), 'fishing' (n = 25000), 'electricity, gas and steam' (n = 23000), 'water transport' (n = 21000), 'manufacture of other chemical products' (n = 19000), 'manufacture of transport equipment' (n = 17000), 'sanitary and similar services' (n = 16000), and 'manufacture of machinery, except electrical' (n = 12000). Despite the total ban of asbestos, about 1500 workers (mainly construction workers and auto mechanics) were reported as having exposure to asbestos on the Finnish Register of Workers Exposed to Carcinogens (ASA Register) in 2006 (Saalo *et al.*, 2006). In 2004, approximately 61000 workers performing demolition and reconstruction work in Germany were registered in the Central Registration Agency for Employees Exposed to Asbestos Dust (Hagemeyer *et al.*, 2006).

Exposure to asbestos in occupational settings is regulated in countries of the EU. According to the European Directive of the EC 2003/18, permissible limits are 0.1 [f/mL] for all types of asbestos, based on an 8-hour time-weighted average (8h-TWA) (EU, 2003). The same limit is in force in most Canadian provinces (Alberta, British Columbia, Manitoba, Ontario, Newfoundland and Labrador, Prince Edward Island, New Brunswick and Nova Scotia); New Zealand; Norway; and, the USA. Other countries have permissible limits of up to 2 fibres/cm^3 (ACGIH, 2007).

Since 1986, the annual geometric means of occupational exposure concentrations to asbestos reported in the OSHA database and the MSHA database have been consistently below the NIOSH recommended exposure limit (REL) of 0.1 f/mL for all major industry divisions in the USA. The number of occupational asbestos exposure samples that were measured and reported by OSHA decreased from an average of 890 per year during 1987–94 to 241 per year during 1995–99. The percentage exceeding the NIOSH REL decreased from 6.3% during 1987–1994 to 0.9% during 1995–99. During the same two periods, the number of exposures measured and reported in the MSHA database decreased from an average of 47 per year during 1987–94 to an average of 23 per year during 1995–99. The percentage exceeding the NIOSH REL decreased from 11.1% during 1987–94 to 2.6% during 1995–99 (NIOSH, 2002a).

Data from studies and reviews of occupational asbestos exposure published since the previous *IARC Monograph* (IARC, 1973) are summarized below.

(a) Studies of occupational exposure

In a mortality study of 328 employees of an asbestos-cement factory in Ontario, Canada, Finkelstein (1983) constructed an exposure model on the basis of available air sampling data, and calculated individual exposure histories to

investigate exposure–response relationships for asbestos-associated malignancies. In retrospectively estimating exposure, the following assumptions were made: exposures did not change during 1962–70, exposures during 1955–61 were 30% higher than the later period, and exposures during 1948–54 were twice as high as during 1962–70. Exposure estimates for the years 1949, 1969, and 1979 were as follows: 40, 20, 0.2 f/mL for the willows operators; 16, 8, 0.5 f/mL for the forming machine operators; and, 8, 4, 0.3 f/mL for the lathe operators.

In an occupational hygiene survey of 24 Finnish workplaces, asbestos concentrations were measured during the different operations of brake maintenance of passenger cars, trucks and buses. During brake repair of trucks or buses, the estimated 8-hour time-weighted average exposure to asbestos was 0.1–0.2 [f/mL]. High levels of exposure (range, 0.3–125 [f/mL]; mean, 56 [f/mL]) were observed during brake maintenance if local exhaust ventilation was not used. Other operations in which the concentration exceeded 1 [f/mL] included cleaning of brakes with a brush, wet cloth or compressed air jet without local exhaust (Kauppinen & Korhonen, 1987).

Kimura (1987), in Japan, reported the following geometric mean concentrations: bag opening and mixing, 4.5–9.5 f/mL in 1970–75 and 0.03–1.6 f/mL in 1984–86; cement cutting and grinding, 2.5–3.5 f/mL in 1970–75 and 0.17–0.57 f/mL in 1984–86; spinning and grinding of friction products, 10.2–35.5 f/mL in 1970–75 and 0.24–5.5 f/mL in 1984–86.

Albin *et al.* (1990) examined total and cause-specific mortality among 1929 Swedish asbestos cement workers employed at a plant producing various products (e.g. sheets, shingles, ventilation pipes) from chrysotile and, to a lesser extent, crocidolite and amosite asbestos. Individual exposures were estimated using dust measurements available for the period 1956–77. Levels of exposure were estimated for the following operations: milling, mixing, machine line, sawing, and grinding. Asbestos concentrations ranged from 1.5–6.3 f/mL in 1956, to 0.3–5.0 f/mL in 1969, and to 0.9–1.7 f/mL in 1975. In all three time periods, the highest concentrations were observed in the milling and grinding operations.

The Health Effects Institute (1991) evaluated an operation and maintenance programme in a hospital on the basis of 394 air samples obtained during 106 on-site activities. The mean asbestos concentration was approximately 0.11 f/mL for personal samples, and approximately 0.012 f/mL for area samples. Eight-hour TWA concentrations showed that 99% of the personal samples were below 0.2 f/mL, and 95% below 0.1 f/mL.

Price *et al.* (1992) estimated the TWAs of asbestos exposures experienced by maintenance personnel on the basis of 1227 air samples collected to measure airborne asbestos levels in buildings with asbestos-containing materials. TWA exposures were 0.009 f/mL for telecommunication switch work, 0.037 f/mL for above-ceiling maintenance work, and 0.51 f/mL for work in utility spaces. Median concentrations were in the range of 0.01–0.02 f/mL.

Weiner *et al.* (1994) reported concentrations in a South African workshop in which chrysotile asbestos cement sheets were cut into components for insulation. The sheets were cut manually, sanded and subsequently assembled. Initial sampling showed personal sample mean concentrations of 1.9 f/mL for assembling, 5.7 f/mL for sweeping, 8.6 f/mL for drilling, and 27.5 f/mL for sanding. After improvements and clean-up of the work environment, the concentrations fell to 0.5–1.7 f/mL.

In a 1985 study, Higashi *et al.* (1994) collected personal and area samples at two manufacturing and processing locations in five Japanese plants manufacturing asbestos-containing products (a roofing material plant; a plant making asbestos cement sheets; a friction-material plant; and two construction and roofing-material plants). Geometric average concentrations of 0.05–0.45

f/mL were measured in area samples, and 0.05–0.78 f/mL in personal samples.

To assess the contribution of occupational asbestos exposure to the occurrence of mesothelioma and lung cancer in Europe, Albin *et al.* (1999) reviewed and summarized the available information on asbestos consumption in Europe, the proportion of the population exposed and levels of exposure. Ranges of exposure were reported for the former Yugoslavia, Poland, and Latvia. In 1987, mean fibre concentrations in Serbia and Montenegro were 2–16 f/mL for textile manufacturing, 3–4 f/mL for friction materials production, and 1–4 f/mL for asbestos cement production. In Poland, exposure levels in 1994 were estimated to be much greater than 2 f/mL in the textile industry, approximately 2 f/mL in asbestos cement and friction-products manufacturing, and greater than 0.5 f/mL in downstream use. In the Latvian asbestos cement industry in 1994, ranges of fibre concentrations were 0.1–1.1 f/mL for the machine line, and 1.1–5.2 f/mL for the milling and mixing areas.

Since 1974, NIOSH has conducted a series of sampling surveys in the USA to gather information on exposure of brake mechanics to airborne asbestos during brake repair. These surveys indicated that the TWA asbestos concentrations (about 1–6 hours in duration) during brake servicing were in the range of 0.004–0.28 f/mL, and the mean TWA concentration, approxiamtely 0.05 f/mL (Paustenbach *et al.*, 2004).

Based on a review of the historical literature on asbestos exposure before 1972 and an analysis of more than 26000 measurements collected during 1972–90, Hagemeyer *et al.* (2006) observed a continual decrease in workplace levels of airborne asbestos from the 1950s to 1990 in Western Germany (FRG) and Eastern Germany (GDR). High concentrations of asbestos fibres were measured for some working processes in Western Germany (e.g. asbestos spraying (400 [f/mL]), removal of asbestos insulations in the ship repair industry (320 [f/mL]), removal of asbestos insulation (300 [f/mL]), and cutting corrugated asbestos sheets (60 [f/mL]), see Table 1.3.

In a study at a large petroleum refinery in Texas, USA, Williams *et al.* (2007a) estimated 8h-TWA asbestos exposures for 12 different occupations (insulators, pipefitters, boilermakers, masons, welders, sheet-metal workers, millwrights, electricians, carpenters, painters, laborers, and maintenance workers) from the 1940s to the 1985 onwards. Estimates were calculated using information on the historical use of asbestos, the potential for exposure due to daily work activities, occupational hygiene sampling data, historical information on task-specific exposures, and use of personal protective equipment. Exposures were estimated for 1940–50, 1951–65, 1966–71, 1972–75, 1976–85, and 1985 onwards. For these time periods, the 8h-TWA exposure (50^{th} percentile) estimates for insulators were, respectively, 9 f/mL, 8 f/mL, 2 f/mL, 0.3 f/mL, 0.005 f/mL, and < 0.001 f/mL. For all other occupations, with the exception of labourers, estimated 8h-TWA exposure estimates were at least 50- to 100-fold less than that of insulators. Estimated 8h-TWA exposure estimates for labourers were approximately one-fifth to one-tenth of those of insulators.

Williams *et al.* (2007b) reviewed historical asbestos exposures (1940–2006) in various non-shipyard and shipyard settings for the following skilled occupations: insulators, pipefitters, boilermakers, masons, welders, sheet-metal workers, millwrights, electricians, carpenters, painters, labourers, maintenance workers, and abatement workers. For activities performed by insulators in various non-shipyard settings from the late 1960s and early 1970s, average task-specific and/or full-shift airborne fibre concentrations ranged from about 2 to 10 f/mL. Average fibre concentrations in US shipyards were about 2-fold greater, and excessively high concentrations (attributed to the spraying of asbestos) were reported in some British Naval shipyards. The introduction of improved occupational hygiene

Table 1.3 Examples of asbestos fibre concentrations in the air (f/cm³) of different workplaces in Germany

Work area		1950–54[a]	1970–74	1980	1990
Textile industries	FRG	100	10	3.8	0.9
	GDR	100	12	6.2	2.2
Production of gaskets	FRG	60	6.6	4.7	0.7
	GDR	60	8.0	7.8	1.6
Production of cement	FRG	200	11	1.1	0.3
	GDR	200	13	1.9	0.7
Production of brake pads	FRG	150	9.1	1.4	0.7
	GDR	150	11	2.4	1.6
Insulation works	FRG	15	15	8.6	0.2
	GDR	18	18	14.0	0.5

[a] Data for the GDR before 1967 are extrapolated
FRG, Federal Republic of Germany; GDR, German Democratic Republic
From Hagemeyer et al. (2006)

practices resulted in a 2- to 5-fold reduction in average fibre concentrations for insulator tasks. The typical range of average fibre concentration for most other occupations was < 0.01–1 f/mL. Concentrations varied with task and time period, with higher concentrations observed for tasks involving the use of powered tools, the mixing or sanding of drywall cement, and the cleanup of asbestos insulation or lagging materials. It was not possible with the available data to determine whether the airborne fibres were serpentine or amphibole asbestos.

Madl *et al.* (2007) examined seven simulation studies and four work-site industrial hygiene studies to estimate the concentration of asbestos fibres to which workers may have historically been exposed while working with asbestos-containing gaskets and packing materials in specific industrial and maritime settings (e.g. refinery, chemical, ship/shipyard). These studies involved the collection of more than 300 air samples and evaluated specific activities, such as the removal and installation of gaskets and packings, flange cleaning, and gasket formation. In all but one of the studies, the short-term average exposures were less than 1 f/mL, and all of the long-term average exposures were less than 0.1 f/mL. Higher short-term average concentrations were observed during the use of powered tools versus hand-held manual tools during gasket formation (0.44 f/mL versus 0.1 f/mL, respectively). Peak concentrations of 0.14 f/mL and 0.40 f/mL were observed during 'gasket removal and flange face cleaning with hand tools' and 'packing removal and installation', respectively.

(b) Dietary exposure

The general population can be exposed to asbestos in drinking-water. Asbestos can enter potable water supplies through the erosion of natural deposits or the leaching from waste asbestos in landfills, from the deterioration of asbestos-containing cement pipes used to carry drinking-water or from the filtering of water supplies through asbestos-containing filters. In the USA, the concentration of asbestos in most drinking-water supplies is less than 1 f/mL, even in areas with asbestos deposits or with asbestos cement water supply pipes. However, in some locations, the concentration in water may be extremely high, containing 10–300 million f/L (or even higher). The average person drinks about 2 litres of water per day (ATSDR, 2001). Risks of exposure to asbestos in drinking-water

may be especially high for small children who drink seven times more water per day per kg of body weight than the average adult (National Academy of Sciences, 1993).

1.6 Talc containing asbestiform fibres

Talc particles are normally plate-like. These particles, when viewed on edge under the microscope in bulk samples or on air filters, may appear to be fibres, and have been misidentified as such. Talc may also form true mineral fibres that are asbestiform in habit. In some talc deposits, tremolite, anthophyllite, and actinolite may occur. Talc containing asbestiform fibres is a term that has been used inconsistently in the literature. In some contexts, it applies to talc containing asbestiform fibres of talc or talc intergrown on a nanoscale with other minerals, usually anthophyllite. In other contexts, the term asbestiform talc has erroneously been used for talc products that contain asbestos. Similarly, the term asbestiform talc has erroneously been used for talc products that contain elongated mineral fragments that are not asbestiform. These differences in the use of the same term must be considered when evaluating the literature on talc. For a more detailed evaluation of talc not containing asbestiform fibres, refer to the previous *IARC Monograph* (IARC, 2010).

1.6.1 Identification of the agent

Talc (CAS No. 14807-96-6) is a designation for both the mineral talc and for commercial products marketed as 'talc', which contain the mineral in proportions in the range of 35% to almost 100%. Commercial talc is classified as 'industrial talc' (refers to products containing minerals other than talc), 'cosmetic talc' (refers to products, such as talcum powder, which contain > 98% talc), and 'pharmaceutical talc' (refers to products containing > 99% talc) (Rohl *et al.*, 1976; Zazenski *et al.*, 1995). Synonyms for talc include: Agalite, French chalk, kerolite, snowgoose, soapstone, steatite, talcite, and talcum.

1.6.2 Chemical and physical properties of the agent

The molecular formula of talc is $Mg_3Si_4O_{10}(OH)_2$. It is a hydrated magnesium sheet silicate mineral, whose structure is composed of a layer of $MgO_4(OH)_2$ octahedra sandwiched between identical layers of SiO_4 tetrahedra. In nature, the composition of talc varies depending on whether or not the magnesium has been substituted with other cations, such as iron, nickel, chromium or manganese (Rohl *et al.*, 1976; IMA, 2005). Pure talc is translucent, appearing white when finely ground (Zazenski *et al.*, 1995). The colour of talc changes in the presence of substituted cations, ranging from pale-green to dark-green, brownish or greenish-grey. Talc has the following chemical and physical properties: melting point, 1500°C; hardness, 1 on the Moh's scale of mineral hardness; density, 2.58–2.83; and cleavage, (001) perfect (Roberts *et al.*, 1974). Talc is a very stable mineral, and is insoluble in water, weak acids and alkalis, is neither explosive nor flammable, and has very little chemical reactivity (IMA, 2005).

Talc's structure is crystalline. It can have a small, irregular plate structure (referred to as microcrystalline talc) or it can have large, well defined platelets (referred to as macrocrystalline talc). Its platyness and crystallinity determine the specific commercial applications for which it is suitable (Zazenski *et al.*, 1995). Talc is formed by complex geological processes acting on pre-existing rock formations with diverse chemical composition (Rohl *et al.*, 1976). Many talc-bearing rocks are formed from magnesia- and silica-rich ultramafic rocks. These rocks have a central core of serpentinite surrounded by successive shells of talc-abundant rock (e.g. talc carbonate and steatite). The serpentinite core is composed mostly of non-asbestiform serpentine minerals (lizardite

and antigorite); however, small amounts of chrysotile asbestos may occur. (Zazenski *et al.*, 1995).

More detail on the chemical and physical properties of talc can be found in the previous *IARC Monograph* (IARC, 2010).

1.6.3 Use of the agent

Talc has several unique chemical and physical properties (such as platyness, softness, hydrophobicity, organophilicity, inertness) that make it desirable for a wide range of industrial and commercial applications (e.g. paint, polymers, paper, ceramics, animal feed, rubber, roofing, fertilizers, and cosmetics). In these products, talc acts as an anti-sticking and anti-caking agent, lubricant, carrier, thickener, absorbent, and strengthening and smoothing filler (IMA, 2005).

In 2000, the worldwide use pattern for talc was as follows: paper industry, 30%; ceramics manufacture, 28%; refractories, 11%; plastics, 6%; filler or pigment in paints, 5%; roofing applications, 5%; cement, 3%; cosmetics, 2%; and other miscellaneous uses, 10% (includes agriculture and food, art sculpture, asphalt filler, autobody filler, construction caulks, flooring, and joint compounds) (Roskill Information Services Ltd, 2003). According to a Mineral Commodity Summary published by the USGS in 2009, talc produced in the USA was used for ceramics, 31%; paper, 21%; paint, 19%; roofing, 8%; plastics, 5%; rubber, 4%; cosmetics, 2%; and other, 10% (Virta, 2009).

No information on the use of asbestiform talc in various industries (apart from mining and milling of talc from deposits containing asbestiform fibres) was identified by the Working Group. For a more detailed description of the uses of talc, refer to the previous *IARC Monograph* (IARC, 2010).

1.6.4 Environmental occurrence

(a) Natural occurrence

Primary talc deposits are found in almost every continent around the world. Talc is commonly formed by the hydrothermal alteration of magnesium- and iron-rich rocks (ultramafic rocks) and by low-grade thermal metamorphism of siliceous dolomites (Zazenski *et al.*, 1995). For more detailed information on the formation of commercially important talc deposits, refer to the previous *IARC Monograph* (IARC, 2010).

Talc deposits whose protoliths are ultramafic rocks (or mafic) are abundant in number but small in total production. They are found in discontinuous bodies in orogenic belts such as the Alps, the Appalachians, and the Himalayas; these types of talc deposits form during regional metamorphism accompanying orogenesis. They also occur in the USA (California, Arkansas, Texas), Germany, Norway, Canada (Ontario and Quebec), southern Spain, Finland, the Russian Federation (Shabry and Miassy), and Egypt. Chlorite and amphibole are usually associated with this type of talc deposit although they are commonly separated in space from the talc ore (Vermont). The amphiboles may or may not be asbestiform, depending on the local geological history (IARC, 2010).

Talc deposits formed from the alteration of magnesian carbonate and sandy carbonate such as dolomite and limestone are the most important in terms of world production. Two types are recognized:

- those derived from hydrothermal alteration of unmetamorphosed or minimally metamorphosed dolomite such as found in Australia (Mount Seabrook and Three Springs); USA (Wintersboro, Alabama; Yellowstone, Montana; Talc City, California; Metaline Falls, Washington; and West Texas); the Republic of Korea; the People's Republic of China; India; the

Russian Federation (Onot); and, northern Spain (Respina)

- those derived from hydrothermal alteration (including retrograde metamorphism) of regionally metamorphosed siliceous dolomites and other magnesium-rich rocks such as in the USA (Murphy Marble belt, North Carolina; Death Valley-Kingston Range, California; Gouverneur District, New York; Chatsworth, Georgia); Canada (Madoc); Italy (Chisone Valley); the Russian Federation (Krasnoyarsk); Germany (Wunsiedel); Austria (Leoben); Slovakia (Gemerska); Spain; France (Trimouns); and Brazil (Brumado) (IARC, 2010).

In a study to examine the amphibole asbestos content of commercial talc deposits in the USA, Van Gosen *et al.* (2004) found that the talc-forming environment (e.g. regional metamorphism, contact metamorphism, or hydrothermal processes) directly influenced the amphibole and amphibole-asbestos content of the talc deposit. Specifically, the study found that hydrothermal talcs consistently lack amphiboles as accessory minerals, but that contact metamorphic talcs show a strong tendency to contain amphiboles, and regional metamorphic talc bodies consistently contain amphiboles, which display a variety of compositions and habits (including asbestiform). Death Valley, California is an example of a contact metamorphic talc deposit that contains accessory amphibole-asbestos (namely talc-tremolite).

1.6.5 Human exposure

(a) Exposure of the general population

Consumer products (e.g. cosmetics, pharmaceuticals) are the primary sources of exposure to talc for the general population. Inhalation and dermal contact (i.e. through perineal application of talcum powders) are the primary routes of exposure. As talc is used as an anti-sticking agent in several food preparations (e.g. chewing gum), ingestion may also be a potential, albeit minor, route of exposure.

As late as 1973, some talc products sold in the USA contained detectable levels of chrysotile asbestos, tremolite, or anthophyllite (Rohl *et al.*, 1976), and it is possible that they remained on the market in some places in the world for some time after that (Jehan, 1984). Some of the tremolite and anthophyllite may have been asbestiform in habit (Van Gosen, 2006).

Blount (1991) examined pharmaceutical- and cosmetic-grade talcs for asbestiform amphibole content using a density-optical method. High-grade talc product samples (n = 15) were collected from deposits in Montana, Vermont, North Carolina, Alabama, and from outside the USA but available in the US market. Samples were uniformly low in amphibole content (with counts in the range of 0–341 particles/mg), and some samples appeared to be completely free of amphibole minerals. In samples containing amphibole minerals, cleavage-type and asbestos-type minerals were observed. Only one sample was found to contain an amphibole particle size distribution typical of asbestos.

More complete information on the levels of exposure experienced by the general population can be found in the previous *IARC Monograph* (IARC, 2010).

(b) Occupational exposure

Inhalation is the primary route of exposure to talc in occupational settings. Exposure by inhalation to talc dust occurs in the talc-producing industries (e.g. during mining, crushing, separating, bagging, and loading), and in the talc-using industries (e.g. rubber dusting and addition of talcs to ceramic clays and glazes). Because industrial talc is a mixture of various associated minerals, occupational exposure is to a mixture of mineral dusts (IARC, 1987b).

In general, data on numbers of workers occupationally exposed to talc are lacking. The

National Occupation Exposure Survey (NOES), which was conducted by the US National Institute for Occupational Safety and Health (NIOSH) during 1981–83, estimated that 1.4 million workers, including approximately 350000 female workers, were potentially exposed to talc in the workplace (NIOSH, 1990). CAREX reports that approximately 28000 workers were exposed to talc containing asbestiform fibres in the workplace within the 15 countries that comprised the EU during 1990–93; however, some major industries producing or using talc were not included.

Many of the early measurements reported very high levels of talc dust exposures in mining and milling operations, often in the range of several mg/m^3, but there is evidence of decreasing exposures (IARC, 1987b; IARC, 2010). For example, before the adoption of technical preventive means in 1950, exposures in the talc operation in the Germanasca and Chisone Valley (Piedmont), Italy, were reported to be approximately 800 mppcf in the mines, and approximately 25 mppcf in the mills. Exposures in both areas were reduced to less than 10 mppcf after 1965 when improved occupational hygiene practices were implemented (Rubino *et al.*, 1976). Although the presence of asbestiform talc was often not reliably verified, it is likely that these levels have also decreased, in part due to mine closures and regulatory controls.

Oestenstad *et al.* (2002) developed a job–exposure matrix for respirable dust, covering all work areas in an industrial grade (tremolitic) talc mining and milling facility in upstate New York, USA. The facility started operating in 1948 with the opening of an underground mine (Mine 1) and a mill (Mill 1). An open pit mine (Mine 2) opened in 1974. Talc from the facility was used predominantly for manufacturing paint and ceramic tiles. The range of all respirable dust concentrations measured in the two baseline exposure surveys was 0.01–2.67 mg/m^3, with an arithmetic mean of 0.47 mg/m^3 and a geometric mean of 0.28 mg/m^3.

Only limited information is available about exposures in secondary industries in which talc is used or processed further. The previous *IARC Monograph* on talc (IARC, 2010) summarizes three historical surveys conducted in these kinds of industries. The IARC Working Group in 1987 noted, however, that even when measurements of respirable fibres were reported, no electron microscopic analysis was conducted to confirm the identity of the fibres. Recently, most industries using talc use non-asbestiform talc (IARC, 2010).

For a more complete description of studies in which occupational exposure to talc and talc-containing products has been reported, refer to the previous *IARC Monograph* (IARC, 2010).

2. Cancer in Humans

2.1 Introduction

The previous *IARC Monographs* were limited to the same six commercial forms of asbestos fibres (chrysotile, actinolite, amosite, anthophyllite crocidolite and tremolite) that are subject of this current evaluation. In the previous *IARC Monograph* (IARC, 1977), the epidemiological evidence showed a high incidence of lung cancer among workers exposed to chrysotile, amosite, anthophyllite, and with mixed fibres containing crocidolite, and tremolite. Pleural and peritoneal mesotheliomas were reported to be associated with occupational exposures to crocidolite, amosite, and chrysotile. Gastrointestinal tract cancers were reported to have been demonstrated in groups occupationally exposed to amosite, chrysotile or mixed fibres containing chrysotile. An excess of cancer of the larynx in occupationally exposed individuals was also noted. Finally the *Monograph* points out that mesothelioma may occur among individuals living in neighbourhoods of asbestos factories

and crocidolite mines, and in persons living with asbestos workers.

Extensive epidemiological research on asbestos has been conducted since then. The associations between asbestos exposure, lung cancer, and mesothelioma have been well established in numerous epidemiological investigations. The epidemiological evidence for other cancer sites is less extensive than it is for lung cancer and mesothelioma, but is still considerable for some. In reviewing these studies, there are some common limitations that need to be borne in mind, which may explain the heterogeneity of the findings from the studies such as:

- The types, fibre sizes and levels of asbestos exposure differed from industry to industry and over time. Most of the heaviest exposures probably occurred in the first two-thirds of the twentieth century in asbestos mining and milling, insulation work, shipyard work, construction, and asbestos textile manufacture. Workers in different industries, eras, and geographic locales were exposed to different types of asbestos fibres, and to fibres of greatly varying dimensions.
- There were differences in how the studies handle the issue of latency or in other words time since first occupational exposure to asbestos. Some studies, especially earlier investigations, accumulated person–years from first exposure, a procedure that may dilute observed risk by including many years of low risk. Others have only accumulated person–years after a certain period of time after first exposure, usually 20 years. Also different studies followed their populations for very different periods of time since first occupational exposure to asbestos.
- The most pervasive problem in interpreting studies was the wide variation among studies in the approaches taken for exposure assessment. Some studies made no attempt to assess exposure beyond documenting employment of study participants in a trade or industry with potential for occupational exposure to asbestos. Other studies used surrogate indices of exposure such as duration of employment or self-reported intensity of exposure, or stratified subjects' exposure by job title. Some used the skills and knowledge of industrial hygienists, obtained direct measurements of asbestos dust levels in air, and developed job–exposure matrices and cumulative exposure indices. Even these analyses are limited by the fact that earlier studies used gravimetric measures of dust exposure, while later used fibre-counting methods based on phase contrast microscopy (PCM). Factors that were used to convert between gravimetric and PCM based measurements are generally unreliable unless they are based on side by side measurements taken in specific industrial operations. Differences in fibre size distributions and fibre type can only be detected using electron microscopy, which has been done in only a very few studies.
- Misclassification of disease was a serious problem for several of the cancer sites. This is particularly true for mesothelioma, which did not have diagnostic category in the ICD system until the 10th review was initiated in 1999.

There were also issues regarding the potential for misclassification of mesotheliomas as colon or ovarian cancers.

For talc that contains asbestiform fibres, previous Working Groups assessed studies on talc described as containing asbestiform tremolite and anthophyllite (IARC, 1987a, b). These fibres fit the definition of asbestos, and therefore a separate review of talc containing asbestiform fibres was not undertaken by this Working Group. The reader is invited to consult the General Remarks

in this volume for further details. For a review of Talc, refer to the previous *IARC Monograph* (IARC, 2010).

2.2 Cancer of the lung

2.2.1 Occupational exposure

Signs that cancer of the lung could be induced by exposure to asbestos was first raised by reports of lung cancer cases that occurred among workers with asbestosis (Gloyne, 1935; Lynch & Smith, 1935). The first cohort study that demonstrated an excess of lung cancer among asbestos exposed workers was a study of textile workers (Doll, 1955). In this study, 11 cases of lung cancer versus 0.8 expected ($P < 0.00001$) were reported based on national mortality rates. Since 1955, an association between lung cancer and occupational exposure to asbestos has been demonstrated in numerous cohort and case–control studies that are summarized in Table 2.1 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-06-Table2.1.pdf, Table 2.2 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-06-Table2.2.pdf, and Table 2.3 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-06-Table2.3.pdf.

Although a causal association between asbestos exposure and lung cancer is generally well recognized, there are still substantial controversies on how the risk might vary by exposure to different fibre types and sizes, and whether there is a risk at low levels of exposure (i.e. environmental exposures). Particularly controversial is the question of whether chrysotile asbestos is less potent for the induction of lung cancer than the amphibole forms of asbestos (e.g. crocidolite, amosite and tremolite), which has sometimes been referred to as the "amphibole hypothesis" (Cullen, 1996; Stayner *et al.*, 1996; McDonald, 1998). This argument is based on the observation from experimental studies that chrysotile asbestos is less biopersistent (i.e. has a shorter half life) in the lung than the amphiboles. Pathological studies of tissue using electron microscopy and energy dispersive analysis of X-rays (EDAX) have been used to measure the amounts of different asbestos fibre types in the lung. Case studies of Canadian chrysotile asbestos workers using these methods have shown an unexpectedly high proportion of amphibole (primarily tremolite) fibres, considering the relatively low percentage of amphibole fibres in commercial chrysotile asbestos (Pooley, 1976; Rowlands *et al.*, 1982; Addison & Davies, 1990). [The Working Group noted that the lower biopersistence of chrysotile in the lung does not necessarily imply that it would be less potent than amphiboles for lung cancer.]

Several meta-analyses have been conducted in which the relative potency of different fibre types and other fibre characteristics have been considered in relation to lung cancer. Lash *et al.* (1997) conducted a meta-analysis based on the findings from 15 cohort studies with quantitative information on the relationship between asbestos exposure and lung cancer risk. The slopes of the lung cancer exposure–response relationship from these studies were analysed using fixed and random effects models. Substantial heterogeneity in the slopes for lung cancer from these studies was found in their analysis. The heterogeneity was largely explained by industry category, dose measurements, tobacco habits, and standardization procedures. There was no evidence in this meta-analysis that differences in fibre type explained the heterogeneity of the slope.

Hodgson & Darnton (2000) performed a meta-analysis based on 17 cohort studies with information on the average level of asbestos exposure for the cohort as a whole or for subgroups in the study. The percentage excess lung cancer risk from each study or subgroup was divided by its average exposure level to derive a slope (RL) for the analysis. Substantial heterogeneity in the findings for lung cancer was also found in this

analysis particularly for the chrysotile cohorts. The heterogeneity in the findings for the chrysotile cohorts was largely attributable to differences in the findings from the studies of chrysotile miners and millers in Quebec (McDonald *et al.*, 1983), and asbestos textile workers in South Carolina (Dement & Brown, 1994; Hein *et al.*, 2007), which differed by nearly 100-fold. No explanation has been found for these extreme differences although several possible explanations have been investigated. Co-exposure to mineral oils in the South Carolina textile plant was proposed as a possible explanation. A nested case–control conducted with the South Carolina cohort failed to provide evidence to support the hypothesis that mineral exposure was associated with an increased risk of lung cancer in this study population (Dement & Brown, 1994). Differences in fibre size distributions have also been considered to be a potential explanation. The asbestos textile industry workers may have used a higher grade of asbestos resulting in exposures to a greater percentage of long fibres than what was experienced by miners and millers in Quebec. A larger percentage of long fibres was found in a recent reanalysis of samples from the South Carolina cohort using transmission electron microscopy (TEM) (Dement *et al.*, 2008) than what was previously reported in TEM analyses of samples from the Quebec mines and mills (Gibbs & Hwang, 1975, 1980). Based on their analysis, Hodgson & Darnton (2000) concluded that the ratio between lung cancer risk for chrysotile and the amphiboles was somewhere between 1:10 and 1:50. However, in their analyses (where they excluded the study of Quebec miners rather than the South Carolina cohort), there was only a 2-fold difference in findings for lung cancer risk between the chrysotile (RL = 2.3) and amphibole cohorts (RL = 4.2). [The Working Group noted that there is no justification for exclusion of the South Carolina cohort because it is one of the highest quality studies in terms of the exposure information used in this study.]

Berman & Crump (2008a) published a meta-analysis that included data from 15 asbestos cohort studies. Lung cancer risk potency factors (Kis = [RR-1]/cumulative exposure) were derived in their analyses that were specific for both fibre type (chrysotile versus amphiboles) and fibre size (length and width). Fibre size information was only available for one of the cohort studies, and for the other studies it was obtained from studies that were conducted in similar industrial settings. As with the previous analyses, substantial variation was found in the findings from these studies with results for lung cancer varying by two orders of magnitude, although no formal statistical tests of heterogeneity were performed. The hypothesis that chrysotile is equipotent as the amphiboles for lung cancer was not rejected for fibres of all widths ($P = 0.07$) or for thick (width > 0.2 μm) fibres ($P = 0.16$). For thin fibres (width < 0.2 μm), there was significant ($P = 0.002$) evidence that chrysotile fibres were less potent than amphiboles. Sensitivity analyses were also conducted in which the South Carolina or Quebec miners and millers cohorts were dropped from the analysis using fibres of all widths. Dropping the South Carolina cohort resulted in a highly significant ($P = 0.005$) result that potency was greater for amphiboles than for chrysotile. Dropping the Quebec cohort resulted in there being no significant ($P = 0.55$) evidence of a difference in potency between the fibre types. [The Working Group noted that both the Hodgson & Darnton and Berman & Crump analyses reveal a large degree of heterogeneity in the study findings for lung cancer, and that findings are highly sensitive to the inclusion or exclusion of the studies from South Carolina or Quebec. The reasons for the heterogeneity are unknown, and until they are explained it is not possible to draw any firm conclusions concerning the relative potency of chrysotile and amphibole asbestos fibres from these analyses.]

Based on findings from experimental studies, it is suspected that long and thin fibres are likely

to be more potent than short and thick fibres in the induction of lung cancer in humans. Unfortunately until recently, all of the epidemiological studies that have been conducted used methods for exposure assessment that did not include a determination of fibre size, and thus this issue could not be directly addressed with these studies. As described above, the meta-analysis conducted by Berman & Crump (2008a) considered the effect of fibre size on lung cancer risk by using data from other studies conducted in similar circumstances as the cohort studies. Their analysis did not reveal strong evidence that lung cancer potency was dependent on fibre size. There was weak evidence that long fibres (length > 10 μm) were more potent than short fibres (5 μm < length < 10 μm) in models using all widths ($P = 0.07$). The lack of size-specific data from the studies was a major limitation of this study with regard to estimating size-specific risk estimates. Stayner *et al.* (2008) published findings from an analysis of the South Carolina asbestos textile cohort in which fibre size specific estimates of lung cancer mortality was evaluated using information from a reanalysis of archived air samples using TEM (Dement *et al.*, 2008). Long fibres (> 10 μm) and thin fibres (< 0.25 μm) were found to be the strongest predictors of lung cancer mortality in this study.

Another study not part of the prior meta-analyses provides relevant information regarding the question of the relative lung cancer potency of the fibre types. Loomis *et al.* (2009) carried out a retrospective cohort mortality study of textile workers from four plants in North Carolina that had never been studied before. Workers in this cohort were primarily exposed to chrysotile asbestos that was imported from Quebec. A small amount of amosite was used in an operation in one of the plants. Overall, an excess of lung cancer was observed in this study (SMR, 1.96; 95%CI: 1.73–2.20), which was very similar in magnitude to that reported in the South Carolina cohort study of textile workers (Hein *et al.*, 2007). However, the slope for the exposure–response between asbestos exposure and lung cancer was considerably lower than that reported in the South Carolina cohort study. The reasons for these differences in the exposure–response relationships are unknown, but one possible reason may be that quality of the exposure information was superior in the South Carolina study, and that the difference could be explained by an attenuation of the slope due to exposure misclassification in Loomis *et al.* (2009).

2.2.2 Environmental exposures

Evidence of an association in women between lung cancer and environmental exposures in New Caledonia to field dust containing tremolite and the use of a whitewash ("po") containing tremolite has been reported (Luce *et al.*, 2000). A positive association with heavy residential exposure to asbestos was observed in a lung cancer case–control study the Northern Province of South Africa, which is a crocidolite and amosite mining area (Mzileni *et al.*, 1999). The association was strongest among women who resided in heavily exposed areas (odds ratio [OR], 5.4; 95%CI: 1.3–22.5; Ptrend = 0.02). A study of lung cancer mortality among women in two chrysotile mining regions of Quebec did not result in an increase in lung cancer (SMR, 0.99; 95%CI: 0.78–1.25) relative to women from 60 other areas of Canada (Camus *et al.*, 1998).

2.2.3 Non-commercial asbestiform amphibole fibres

There is emerging epidemiological evidence that non-commercial amphibole fibres that are asbestiform have carcinogenic potential. These fibres are not technically "asbestos," and they were never commercially marketed. However, the Working Group felt it was important to discuss the recent evidence concerning these

fibres because of their similarity to asbestos, and because of public concerns regarding this issue.

Several studies have described adverse health associations with the amphibole fibres that contaminated vermiculite mined in Libby, Montana, USA. These fibres were originally characterized as from the tremolite-actinolite series (IARC, 1987a), however, they have been more recently described by the US Geological Society as approximately 84% winchite, 11% richterite, and 6% tremolite (Meeker *et al.*, 2003). Sullivan (2007) reported standardized mortality ratios (SMRs), using cause of death data and expected mortality for the underlying cause of death based on national age-, race-, and sex-specific rates. Using a 15-year exposure lag, there were increased SMRs for all cancer (SMR, 1.4; 95%CI: 1.2–1.6; $n = 202$), and lung cancer (SMR, 1.7; 95%CI: 1.4–2.1; $n = 89$). Increasing risks were observed across categories of cumulative exposure; the SMR estimates were 1.5, 1.6, 1.8, and 1.9 in the 1–4.49, 4.5–22.9, 23.0–99.0, and ≥ 100 f/mL–years exposure categories, respectively. Results from other studies (Amandus *et al.*, 1987; McDonald *et al.*, 2004) of analyses using a continuous measure of exposure also resulted in statistically significant relationships with lung cancer mortality risk. For example, in the updated analysis by McDonald *et al.* (2004), the estimated linear increase in relative risk of respiratory cancer risk per 100 f/mL–years cumulative exposure was 0.36 (95%CI: 0.03–1.2; $P = 0.02$).

2.3 Mesothelioma

Pleural and peritoneal mesotheliomas are very rare malignancies that occur in the mesothelial cells that line these cavities. The first report of a possible association between asbestos exposure and mesothelioma was by Wagner *et al.* (1960) who described an outbreak of mesothelioma in a crocidolite mining region of South Africa. The majority of the cases reported had worked in the mines (23/33) but some of the cases had also occurred among individuals with no history of occupational exposures (10/33). Since then, an excess of mesothelioma has been observed in a large number of cohort and case–control studies (summarized in online Tables 2.2, 2.3 and Table 2.4 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-06-Table2.4.pdf) in a variety of different industries using and producing asbestos. Although the causal association between mesothelioma and asbestos has been well established, several important issues remain to be resolved that are discussed below.

2.3.1 Fibre type

Although all forms of asbestos can cause mesothelioma, there is considerable evidence that the potency for the induction of mesothelioma varies by fibre type, and in particular that chrysotile asbestos is less potent than amphibole forms of asbestos. An excess of mesothelioma has been reported in cohort studies of chrysotile exposed miners and millers in Quebec (Liddell *et al.*, 1997), and in South Carolina asbestos textile workers who were predominantly exposed to chrysotile asbestos imported from Quebec (Hein *et al.*, 2007). However, the fact that the chrysotile asbestos mined in Quebec is contaminated with a small percentage (< 1.0%) of amphibole (tremolite) asbestos has complicated the interpretation of these findings. McDonald *et al.* (1997) found in a nested case–control study for mesothelioma in the Thetford mines of Quebec that an association with asbestos exposure was evident in mines from a region with higher concentrations of tremolite, and not in another region with lower concentrations of tremolite. Bégin *et al.* (1992) noted that although tremolite levels may be 7.5 times higher in Thetford than in Asbestos, the incidence of mesothelioma in these two Quebec mining towns was proportional to the size of their workforce. This suggests that the tremolitic content of the ores may not be a

determinant of mesothelioma risk in Quebec. Separate analyses for workers at the Thetford and Asbestos mines and mills did not demonstrate a different exposure–response relationship for asbestos and mesothelioma in the two mining areas (McDonald & McDonald, 1995).

In a mesothelioma case–control study in South Africa, an association was reported with exposures to crocidolite and amosite asbestos, but no cases were found to have been exclusively exposed to chrysotile asbestos (Rees *et al.*, 1999). One possible explanation for these negative findings for chrysotile is that South African chrysotile asbestos may contain relatively little tremolite (Rees *et al.*, 1992). Another possible explanation is that chrysotile mining began later, and production levels were lower than in the crocidolite and amosite mines of South Africa. Cases of mesothelioma have been reported among asbestos miners in Zimbabwe, which has been reported to be uncontaminated with tremolite asbestos (Cullen & Baloyi, 1991). Excess mesothelioma mortality (standardized incidence ratio [SIR], 4.0, 95%CI: 1.5–8.7) was reported in miners and millers from a chrysotile mine in Balangero, Italy (Mirabelli *et al.*, 2008), reportedly free of amphibole contamination (Piolatto *et al.*, 1990).

An evaluation of the relative potency of the different fibre types of asbestos has been considered in the meta-analyses that were previously described (see prior section on lung cancer) by Hodgson & Darnton (2000) and Berman & Crump (2008a, b). Hodgson & Darnton (2000) used the percentage of mesothelioma deaths of all deaths expected (at an age of first exposure of 30) per unit of cumulative exposure (Rm) as the measure for their analysis. They computed separate estimates of Rm for crocidolite, amosite and chrysotile asbestos. Based on their analyses, they estimated that the ratio of the potency for mesothelioma (pleural and peritoneal combined) was 1:100:500 for chrysotile, amosite, and crocidolite respectively.

The meta-analysis conducted by Berman & Crump (2008a) was based on the analysis of the slopes (Km) that were estimated using an approach that assumes that the mortality rate from mesothelioma increases linearly with the intensity of exposure, and for a given intensity, increases indefinitely after exposure ceases, approximately as the square of time since first exposure (lagged 10 years). This model was tested with the raw data from several studies, and found to provide a good fit to the data (Berman & Crump, 2008b). Regression models were fitted to the study Km values that included information from surrogate studies to estimate fibre type (chrysotile versus amphiboles) and fibre length (short versus long) specific potency slopes (Berman & Crump, 2008a). Alternative models were fitted with exposure metrics based on different fibre widths. The hypothesis that chrysotile and amphibole forms of asbestos are equipotent was strongly rejected, and the hypothesis that potency for chrysotile asbestos was 0 could not be rejected based on their models ($P < 0.001$ and $P = 0.29$, respectively, for all-widths model). The best estimates for the relative potency of chrysotile ranged from zero to about 1/200th that of amphibole asbestos (depending on the width of the exposure metric used in the model). [The Working Group noted that there is a high degree of uncertainty concerning the accuracy of the relative potency estimates derived from the Hodgson & Darnton and Berman & Crump analyses because of the severe potential for exposure misclassification in these studies.]

Two newer studies, not part of the prior meta-analyses, provide important information regarding the question of the relative potency of the fibre types. The first is a study of a cohort of textile workers in North Carolina not previously examined (Loomis *et al.*, 2009). Workers in this cohort were primarily exposed to chrysotile asbestos imported from Quebec. A relatively large excess of both mesothelioma [SMR, 10.92; 95%CI: 2.98–27.96] and pleural cancer [SMR,

12.43; 95%CI: 3.39–31.83]. The pleural and mesothelioma deaths combined comprised 0.3% of all deaths. This percentage was nearly identical to the estimate developed for the chrysotile cohorts in a review article by Stayner *et al.* (1996). Based on the approach that Hodgson & Darnton used in their meta-analysis, the authors estimated that the percentage of deaths per unit of fibre exposure was 0.0058% per f–y/mL (0.0098% per f–y/mL for workers followed ≥ 20 years). This estimate was considerably higher than the estimate developed by Hodgson & Darnton of 0.0010% per f–yr/mL for cohorts exposed to chrysotile.

The other study investigated mesothelioma among chrysotile miners and millers, and resident communities in Balangero, Italy. The chrysotile mined at Balangero was reported to be free of tremolite and other amphiboles. The ore contains trace amounts of another fibre called blangeroite, which is not an amphibole (Turci *et al.*, 2009). A previous cohort of the miners and millers in Balangero with follow up to 1987 identified only two deaths from mesothelioma (Piolatto *et al.*, 1990). Cases of mesothelioma were identified from a local mesothelioma registry comprises people who had been mine employees; employees of subcontractors or other firms transporting or refining Balangero asbestos, asbestos ore; residents of the area who were exposed from air pollution, living with a mine employee or from mine tailings from Balangero. Six cases of mesothelioma were identified among blue-collar miners, and an estimated 1.5 deaths (SIR, 4.00; 95%CI: 1.47–8.71) would be expected based on a previous cohort study (Piolatto *et al.*, 1990), and conservative assumptions about the cohort. Additional cases of mesothelioma were identified among white-collar miners (three cases), workers in the mine hired by subcontractors (five cases), and from non-occupational exposures or exposure to re-used tailings (ten cases). Expected numbers of mesothelioma cases could not be derived for these groups because they were not part of the original cohort definition. The findings from this investigation indicate that the previous risk of mesothelioma for the Balangero cohort were seriously underestimated.

2.3.2 Fibre size

Based on a review of toxicological and human studies, Lippmann (1990) suggested that fibres shorter than 0.1 μm and longer than 5 μm are related to mesothelioma in humans. The Berman & Crump meta-analyses provided weak evidence that fibre length is a determinant of the potency of asbestos. The test of the hypothesis that long fibres (length ≥ 10 μm) and short fibres (5 < length < 10 μm) are equipotent was nearly rejected in some models (e.g. $P = 0.09$ for all widths). Thus, their findings provide weak support that long fibres may be more potent than short fibres for mesothelioma. There was little evidence in their analyses that thin fibres (width < 0.4 or < 0.2 μm) were stronger predictors of mesothelioma potency than all fibre widths combined. A major limitation of their analysis was that it relied on surrogate data to estimate the fibre-size distributions for the studies used in the meta-analysis.

2.3.3 Pleural versus peritoneal tumours

The ratio of pleural to peritoneal mesotheliomas has varied considerably in different epidemiological studies of asbestos-exposed cohorts. In the cohort studies included in the meta-analysis conducted by Hodgson & Darnton (2000), the percentage of mesotheliomas that were peritoneal varied from 0 to over 50%. Hodgson & Darnton reported that peritoneal mesotheliomas increased with the square of cumulative exposure to asbestos (i.e. a supralinear relationship); whereas pleural mesotheliomas increased less than linearly with cumulative exposure to asbestos. This implies that the number of peritoneal mesotheliomas would dramatically increase relative to the number of pleural mesotheliomas at high asbestos exposure levels. Welch *et al.*

(2005) found a strong association (OR, 5.0; 95%CI: 1.2–21.5) between asbestos exposure and peritoneal cancer in a population-based case–control study. This study included a large percentage of men with what were judged to be low exposures to asbestos.

2.3.4 Environmental exposures

An excess of mesothelioma has been observed in several studies of communities with environmental exposure to asbestos. A large excess of mesothelioma was reported in a study of people living in villages in Turkey exposed to erionite used to whitewash their homes (Baris *et al.*, 1987). An excess in mesothelioma was reported among people living near crocidolite mining regions in South Africa and Western Australia (Wagner & Pooley, 1986), among people residing in areas of tremolite contamination in Cyprus (McConnochie *et al.*, 1987) and New Caledonia (Luce *et al.*, 2000), and with non-occupational exposures in Europe (Magnani *et al.*, 2000), Italy (Magnani *et al.*, 2001), and California (Pan *et al.*, 2005).

Mesothelioma has also been reported to occur among household members of families of asbestos workers (Anderson *et al.*, 1976; Ferrante *et al.*, 2007).

2.3.5 Non-commercial asbestiform fibres

Several studies have described adverse health associations with the amphibole fibres that contaminated vermiculite mined in Libby, Montana, USA. These fibres were originally characterized as from the tremolite-actinolite series (IARC, 1987a); however, they were subsequently described by the US Geological Society as being composed of approximately 84% winchite, 11% richterite, and 6% tremolite (Meeker *et al.*, 2003). Sullivan (2007) reported SMRs, using cause of death data and expected mortality for the underlying cause of death based on national age-, race-, and sex-specific rates. Using a 15-year exposure lag, there were increased SMRs, mesothelioma defined by ICD-10 for deaths after 1999 (SMR, 14.1; 95%CI: 1.8–54.4; n = 2) and pleural cancer (SMR, 23.3; 95%CI: 6.3–59.5; n = 4). The only exposure–response modelling of mesothelioma was presented in the paper by McDonald *et al.*, based on 12 mesothelioma cases (McDonald *et al.*, 2004). Using Poisson regression, the mesothelioma mortality rate across increasing categories of exposure was compared with the rate in the lowest exposure category. For the cumulative exposure metric, the relative risk estimates were 1.0 (referent), 3.72, 3.42, and 3.68, based on 1, 4, 3, and 4, cases, respectively. The mean exposure level in these four quartiles was 8.6, 16.7, 53.2, and 393.8 f/mL–yr, respectively. It should be noted that the referent group was also at excess risk of dying from mesothelioma, i.e. there were 1–3 cases of mesothelioma observed in the referent group, which may have attenuated the observed effects.

A high incidence of mesothelioma was reported among residents of Biancavilla, Italy, a city in eastern Sicily (SMR, 7.21; 95%CI: 3.59–13.00). Reviewing of the work histories of the cases did not indicate an occupational explanation for these exposures, and thus environmental explanations for the mesothelioma excess were sought. Environmental studies have indicated that these mesotheliomas are most likely due to exposures to fluoro-edenite which is a newly recognized fibre that is very similar in morphology and composition to the tremolite-actinolite series (Comba *et al.*, 2003; Bruno *et al.*, 2006; Putzu *et al.*, 2006).

2.4 Other cancer sites

Beyond lung cancer and mesothelioma, the body of literature examining associations between asbestos and other cancers is more sparse. This reflects the fact that lung cancer and mesothelioma have been the principal areas of research

until relatively recently, and other cancers were often not considered in detail in published reports. Clinical and epidemiological studies that span the past five decades suggest, however, that asbestos may be associated with other cancers in addition to lung cancer and mesothelioma. To examine these associations in detail, the US IOM (2006) published a report evaluating the evidence relevant to causation of cancer of the pharynx, larynx, oesophagus, stomach, colon and rectum by asbestos. The present analysis draws on the IOM analysis and presents the most significant positive and negative studies for each anatomical site, with an emphasis on studies that presented data on dose–response as well as on published meta-analyses. Additionally, the present analysis examines the association between asbestos exposure and ovarian cancer, an association that was not examined by the IOM.

2.4.1 Cancer of the pharynx

See Table 2.5 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-06-Table2.5.pdf.

(a) Cohort Studies

The Working Group examined 16 cohort studies of asbestos and cancer of the pharynx. Some of these studies examined all cancers of the lips, oral cavity, and pharynx. Others restricted their examination to the pharynx itself. Two studies examined only cancers of the hypopharynx. The main findings are summarized in the following paragraphs.

Selikoff & Seidman (1991) observed an SMR for cancer of the oropharynx of 2.18 (95%CI: 1.62–2.91) among a cohort of 17800 male asbestos insulation workers across the USA and Canada. This is the cohort study with the largest number of deaths from pharyngeal cancer, a total of 48 deaths.

Piolatto *et al.* (1990) observed an SMR for cancer of the oropharynx of 2.31 (95%CI: 0.85–5.02; based on six deaths) in a cohort of 1058 asbestos miners in northern Italy exposed to chrysotile asbestos. No association was seen in this cohort between duration of occupational exposure to asbestos and risk of cancer of the pharynx.

Reid *et al.* (2004) observed an SMR for cancer of the pharynx of 1.88 (95%CI: 1.15–3.07; based on 16 deaths) in a cohort of 5685 crocidolite asbestos miners and millers in Western Australia.

Sluis-Cremer *et al.* (1992) observed an SMR for cancer of the lip, oral cavity and pharynx of 2.14 (95%CI: 1.03–3.94; based on 10 deaths) in a cohort of 7317 male asbestos miners in South Africa, some exposed to crocidolite and others to amosite. Cancer of the pharynx was defined in this population as cancer of the lip, oral cavity or pharynx. There was no excess mortality for cancer of the pharynx in the subcohort of amosite asbestos miners (SMR, 0.42; 95%CI: 0.00–1.97), but in the subcohort of crocidolite asbestos miners, the SMR for cancer of the pharynx was 2.94 (95%CI: 1.16–6.18).

Pira *et al.* (2005) observed an SMR for cancer fo the pharynx of 2.26 (95%CI: 0.90–4.65; based on seven deaths) in a cohort of 1996 workers in the asbestos textiles industry in Italy.

Other cohort studies of populations occupationally exposed to asbestos in a range of industries contained only small numbers of deaths from cancer of the pharynx (most < 10 deaths), were generally non-positive in their findings, and reported little evidence for dose–response relationships.

(b) Case–control studies

Case–control studies examining the association between asbestos exposure and cancer of the pharynx have two advantages over cohort studies:

1. they are able to collect more cases of this relatively uncommon malignancy; and
2. they are able to adjust for alcohol and tobacco consumption, the two most common causes

of cancer of the pharynx in developed and developing countries.

The present review included six case–control studies. Four of them adjusted for alcohol and tobacco consumption. The main findings are summarized in the following paragraphs.

Marchand *et al.* (2000) carried out a hospital-based, case–control study of 206 cases of cancer of the hypopharynx and 305 controls in France, and found a relative risk of 1.80 (95%CI: 1.08–2.99) in the 161 of their cases ever exposed to asbestos, adjusted for exposure to tobacco and alcohol.

Berrino *et al.* (2003) conducted a multicentre, case–control study of cancer of the hypopharynx in Europe, and found an odds ratio (OR) for "probable" exposure to asbestos of 1.8 (95%CI: 0.6–5.0). This study was restricted to analyses of cancers of the hypopharynx. For cases with "possible" exposure to asbestos, the odds ratio was 1.80 (95%CI: 0.90–3.90). These odds ratios were adjusted for exposure to tobacco and alcohol.

Zheng *et al.* (1992) conducted a population-based, case–control study of cancer of the pharynx in Shanghai, the People's Republic of China, with 204 incident cancer cases and 414 controls. The relative risk for asbestos exposure was 1.81 (95%CI: 0.91–3.60). Cigarette smoking and alcohol consumption were observed to be positively associated with cancer fo the pharynx. By contrast, increasing intake of certain fruits and vegetables, notably oranges, tangerines and Chinese white radishes, appeared to be associated with a reduced risk for cancer of the pharynx.

(c) *Meta-analyses*

The IOM (2006) conducted a meta-analysis of the published cohort studies examining the association between asbestos exposure and cancer of the pharynx. The IOM noted that the findings of the cohort studies were consistently positive. They calculated that the "estimated aggregated relative risk of cancer of the pharynx from any exposure to asbestos was 1.44 (95%CI: 1.04–2.00). "The IOM noted that few studies had evaluated dose–response trends, and that there was no indication of higher risks associated with more extreme exposures."

The IOM also conducted a meta-analysis of the case–control studies examining the association between asbestos exposure and cancer of the pharynx. The IOM reported the summary relative risk for cancer of the pharynx in people with "any" exposure to asbestos compared to people with no exposure to be 1.5 (95%CI: 1.1–1.7). The IOM observed that the studies were inconsistent, and that there was little evidence for a dose–response relationship.

2.4.2 *Cancer of the larynx*

See Table 2.5 online.

Cancer of the larynx in relation to asbestos exposure has been studied in a large number of cohort and case–control studies undertaken among occupationally exposed populations in North and South America, Europe, and Asia. (IOM, 2006).

(a) *Cohort studies*

Cohort studies of workers exposed occupationally to asbestos have found evidence for an association between asbestos exposure and cancer of the larynx across a broad range of industries. The Working Group reviewed 29 cohort studies encompassing 35 populations exposed to asbestos. Noteworthy findings from among these studies are summarized in the following paragraphs.

Selikoff & Seidman (1991) found an SMR for cancer of the larynx of 1.70 (95%CI: 1.01–1.69) among 17800 male insulation workers in the USA and Canada.

Musk *et al.* (2008) found an SMR for cancer of the larynx of 1.56 (95%CI: 0.83–2.67) among 6943 asbestos miners and millers from Western Australia, exposed predominantly to crocidolite

asbestos, when all cohort members lost to follow-up were assumed to be alive. When the analysis was re-run censoring all subjects at the date last know to be alive, the SMR was 2.57 (95%CI: 1.37–4.39).

Reid *et al.* (2004) carried out a study of cancer incidence in this same Australian cohort, and found a significant increase in incidence of cancer of the larynx (SIR, 1.82; 95%CI: 1.16–2.85).

Piolatto *et al.* (1990) found an SMR for cancer of the larynx of 2.67 (95%CI: 1.15–5.25; based on eight deaths) in a cohort study of 1058 male asbestos miners in northern Italy. In the subset of this cohort with > 20 years' exposure to asbestos, the SMR for cancer of the larynx was 4.55 (95%CI: 1.47–10.61). There was evidence of a positive dose–response relationship between cumulative exposure to asbestos dust, measured as fibre–years, and risk of death from cancer of the larynx. The SMRs for cancer of the larynx were 1.43 (95%CI: 0.04–7.96) in workers with exposure < 100 fibre–years; 2.22 (95%CI: 0.27–8.02) in workers with exposure of 100–400 fibre–years; and 3.85 (95%CI: 1.25–8.98) in workers with cumulative exposure > 400 fibre–years.

Peto *et al.* (1985) found an overall SMR for cancer of the larynx of 1.55 (95%CI: 0.42–3.97; based on four deaths) in a cohort of 3211 asbestos-textile workers in the United Kingdom. When workers were subdivided according to time since first employment, and by duration of employment in "scheduled" (asbestos-exposed) areas of the plant, four deaths from cancer of the larynx were observed in the most heavily exposed group versus 1.53 expected (SMR, 2.55).

Pira *et al.* (2005) found an overall SMR for cancer of the larynx of 2.38 (95%CI: 0.95–4.90; based on seven deaths–all of them in male workers) in a cohort of 889 men and 1077 women employed in an asbestos textiles plant in Italy.

Raffn *et al.* (1989) found an overall SIR for cancer of the larynx of 1.66 (95%CI: 0.91–2.78) in a cohort study of 7986 men and 584 women employed in the asbestos-cement industry in Denmark However, in the subset with > 5 years employment, the SIR was 2.27 (95%CI: 0.83–4.95), and in the group first employed from 1928–40, the SIR was 5.50 (95%CI: 1.77–12.82).

(b) Case–control studies

Case–control studies are important in examining relationships between asbestos exposure and cancer of the larynx, because they overcome the relative rarity of the diagnosis in cohort studies, and also because they permit consideration of potential confounding by exposure to tobacco and alcohol, the two most important risk-factors for this malignancy in developed and developing countries.

The Working Group analysed 15 case–control studies of asbestos and cancer of the larynx. This analysis revealed that 14 of the 15 published studies had found evidence for a significantly positive association between asbestos exposure and cancer of the larynx; only one study (Luce *et al.*, 2000) reported an odds ratio below 1.0.

(c) Meta-analyses

The IOM conducted a meta-analysis of cohort studies examining the association between asbestos exposure and cancer of the larynx. For studies examining "any" versus no exposure, the summary relative risk was 1.4 (95%CI: 1.19–1.64). For studies comparing "high" exposure versus no exposure, the lower bound summary relative risk was 2.02 (95%CI: 1.64–2.47), and the upper bound summary relative risk was 2.57 (95%CI: 1.47–4.49).

The IOM also conducted a meta-analysis of the published case–control studies examining the association between asbestos exposure and cancer of the larynx (IOM, 2006). This meta-analysis calculated a summary relative risk of 1.43 (95%CI: 1.15–1.78), before adjusting for consumption of tobacco and alcohol. After adjusting for tobacco and alcohol consumption, the association of cancer of the larynx with

asbestos exposure persisted, with an adjusted summary relative risk of 1.18 (95%CI: 1.01–1.37).

2.4.3 Cancer of the oesophagus

See Table 2.6 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-06-Table2.6.pdf.

(a) Cohort studies

The Working Group examined 25 studies of cohorts occupationally exposed to asbestos. Notable findings from among these studies are:

Selikoff & Seidman (1991) found an SMR for cancer of the oesophagus of 1.61 (95%CI: 1.13–2.40) among a cohort of 17800 asbestos insulations workers across the USA and Canada. Selikoff & Seidman (1991) observed that cancer in asbestos workers is "very much related to latency," with most of the increased risk occurring only 25 or more years from the onset of occupational exposure to asbestos.

In a cohort of 10939 male and 440 female asbestos miners and millers in Quebec, Canada, exposed predominantly to chrysotile asbestos, followed through 1975, McDonald *et al.* (1980) reported that mortality for cancer of the oesophagus and stomach (the two were combined) was elevated (SMR, 1.27). Further follow-up through 1988 of a subset of this cohort, consisting of 5335 men, examined esophageal cancer mortality separate from stomach cance,r and found no excess mortality (SMR, 0.73; 95%CI: 0.35 – 1.34) (McDonald *et al.*, 1993).

Musk *et al.* (2008) found an SMR for cancer of the oesophagus was 1.01 (95%CI: 0.71–1.40) in a cohort study of 6943 asbestos miners from Western Australia followed through 2000, exposed predominantly to crocidolite asbestos, when all cohort members lost to follow-up were assumed to be alive. When the analysis was re-run censoring all subjects at the date last known to be alive, the SMR was 1.20 (95%CI: 0.62–2.10).

Hein *et al.* (2007) found an SMR for cancer of the oesophagus of 1.87 (95%CI: 1.09–2.99) in a cohort of 3072 asbestos textile workers in South Carolina, occupationally exposed to chrysotile asbestos and followed through 2001.

Peto *et al.* (1985) found 11 deaths from cancer of the oesophagus versus 6.59 expected (SMR = 1.67; 95%CI: 0.83–2.99) in a cohort of 3211 male asbestos textile workers in the United Kingdom. For the subset of workers with 10+ years employment in "scheduled" (asbestos-exposed) areas of the plant and with 20+ years since first employment, the SMR for cancer of the oesophagus was 2.36 (95%CI: 0.49–6.91). For all workers in this cohort with < 20 years since first employment, two deaths for cancer of the oesophagus was observed versus 2.18 expected, and for workers with 20+ years since first employment, there were nine deaths from cancer of the oesophagus versus 4.4 expected (see Table 6 in Peto *et al.*, 1985).

Berry *et al.* (2000) found a 2-fold excess mortality for cancer of the oesophagus (SMR, 2.08; 95%CI: 1.07–3.63) among a cohort of over 5000 asbestos-exposed factory workers in the east end of London, United Kingdom, who had produced asbestos insulation boards, and who were followed for 30+ years. In the subset of workers within this population with "severe" asbestos exposure of more than 2 years' duration, the SMR for cancer of the oesophagus was 5.62 (95%CI: 1.82 – 13.11). And in the subset of women with "severe" exposure to asbestos of > 2 years, the SMR for cancer of the oesophagus was 9.09 (95%CI: 1.10–32.82).

Other cohort studies of various groups occupationally exposed to asbestos – asbestos-cement workers, friction products workers, and "generic" asbestos workers – yield generally non-positive results for cancer of the oesophagus.

(b) Case–control studies

The Working Group examined five case–control studies that examined the association between asbestos exposure and cancer of the oesophagus.

A case–control study in Quebec, Canada found an OR of 2.0 (95%CI: 1.1–3.8) for any exposure to asbestos among 17 patients diagnosed with squamous cell carcinoma of the oesophagus. (Parent *et al.*, 2000).

A case–control study conducted within a cohort of nearly 400000 Swedish construction workers found evidence for a positive association between asbestos exposure and adenocarcinoma of the oesophagus. Relative risk increased from 1.0 (reference) among workers with no asbestos exposure, to 1.7 (95%CI: 0.5–5.4) among those with "moderate" exposure, and to 4.5 (95%CI: 1.4–14.3) among those workers with "high" asbestos exposure, thus suggesting a positive dose–response relationship (Jansson *et al.*, 2005).

(c) Meta-analyses

Meta-analyses have been undertaken of the association between asbestos exposure and cancer of the oesophagus:

A meta-analysis by Frumkin & Berlin (1988) stratified studies according to SMR for lung cancer and also according to the percentage of deaths due to mesothelioma. The rationale is that a higher death rate for either lung cancer or mesothelioma is taken to be a surrogate index of higher cumulative exposure to asbestos. However, no association was observed between death rate for cancer of the oesophagus in the published cohorts by either lung cancer SMR or percentage of death for mesothelioma.

Meta-analyses by Edelman (1988) and by Goodman *et al.* (1999) did not detect an association between asbestos exposure and cancer of the oesophagus.

A meta-analysis by Morgan *et al.* (1985) that examined earlier studies, which tended to have heavier exposure, found a summary SMR for cancer of the oesophagus in asbestos-exposed workers of 2.14 (95%CI: 1.326–3.276). When cases of cancer of the oesophagus based on "best evidence" (pathological review) were deleted from these cohorts, the SMR remained elevated at 2.38 (95%CI: 1.45–3.68).

The IOM (2006) conducted a meta analysis of 25 cohort studies and reported a summary relative risk of 0.99 (95%CI: 0.78–1.27) for any exposure to asbestos versus no exposure. The IOM also examined the relative risk of "high" versus no exposure, and calculated a lower bound summary relative risk of 1.35 (95%CI: 0.81–2.27), and a higher bound summary relative risk of 1.43 (95%CI: 0.79–2.58). The IOM determined that there were too few case–control studies to permit a meta-analysis.

2.4.4 Cancer of the stomach

The Working Group reviewed 42 cohort studies and five population-based case–control studies that examined the association between asbestos and cancer of the stomach (See Table 2.6 online).

(a) Cohort studies

Notable findings among the cohort studies are:

Selikoff *et al.* (1964) reported a nearly 3-fold excess mortality for cancer of the stomach (12 observed versus 4.3 expected) in a population of 632 insulation workers in New York and New Jersey occupationally exposed to asbestos dust. Further analysis within this cohort (Selikoff *et al.*, 1979) found evidence of a dose–response relationship between duration of exposure to asbestos (in years), and risk of death from cancer of the stomach. The SMR for cancer of the stomach increased from 0.00 in workers exposed for < 20 years, to 4.00 (95%CI: 1.47 – 8.71) in those exposed for 20 –35 years, and to 3.42 (95%CI: 1.82 – 5.85) in those exposed for > 35 years.

Selikoff *et al.* (1967) found a modest, non-significant increase in risk of death for cancer of the stomach: 34 observed v. 29.4 expected, (SMR = 1.16;95%CI: 0.92 – 1.78) in a larger cohort study of 17800 insulation workers across the USA and Canada. No data on dose–response for cancer of the stomach were presented in this analysis.

Liddell *et al.* (1997) reported an overall SMR for cancer of the stomach of 1.24 (95%CI: 1.07 –1.48) in a study of 10918 asbestos miners and millers exposed predominantly to chrysotile asbestos, in Quebec, Canada. Within this cohort, a positive dose–response relationship was observed between cumulative exposure to asbestos dust (mcpf-year) and mortality for cancer of the stomach. Thus, for workers with cumulative dust exposure < 300, the SMR was 1.16; for workers with cumulative exposure of 300 – 400, the SMR was 1.29; for workers with cumulative exposure of 400 – 1000, the SMR was 1.21; and for workers in the highest exposure category, with cumulative exposure > 1000, the SMR was 3.21 (95%CI: 1.87 –5.14). An additional finding in this cohort was a modest interaction between cumulative asbestos exposure, cigarette smoking, and mortality from cancer of the stomach.

Musk *et al.* (2008) found an SMR for cancer of the stomach of 1.01 (95%CI: 0.71 – 1.40) in a cohort of 6943 asbestos miners and millers exposed predominantly to crocidolite asbestos in Wittenoom, Western Australia, followed through the end of 2000, and when all cohort members lost to follow-up were assumed to be alive. When the analysis was re-run censoring subjects at the date last known to be alive, the SMR was 1.71 (95%CI: 1.20–2.35).

Reid *et al.* (2004) conducted a nested case–control study within this same Australian cohort, and found a positive exposure-response relationship between cancer of the stomach and cumulative exposure to asbestos (test for trend, P = 0.057). No association was seen between cancer of the stomach and either time since first exposure or year of starting work with asbestos. Smoking status was associated with cancer of the stomach, but not significantly.

Meurman *et al.* (1974) found a non-significant increase in SMR for cancer of the stomach: SMR = 1.42 (95%CI: 0.76 – 2.43) in a cohort of 736 asbestos miners in Finland exposed to anthophyllite asbestos.

Berry *et al.* (2000) found a modest, non-significant increased risk for death from cancer of the stomach: 28 observed versus 23.1 expected (SMR, 1.21; 95%CI: 0.81–1.75) in a British study of factory workers producing asbestos insulation in the east end of London.

Strongly positive dose–response associations between cumulative asbestos response and cancer of the stomach were observed in two cohort studies of Chinese factory workers – one in Beijing and the other in Qingdao; relative risks for cancer of the stomach were 4.4 and 2.4, respectively (Zhu & Wang, 1993; Pang *et al.*, 1997).

Raffn *et al.* (1989) observed 43 deaths from cancer of the stomach versus 30.09 expected (SMR, 1.43; 95%CI: 1.03 – 1.93) in a cohort of 7986 men employed from 1928–84 in the asbestos cement industry in Denmark.

Enterline *et al.* (1987) observed a SMR for cancer of the stomach of 1.80 (95%CI: 1.10–2.78) in a cohort of 1074 retired US asbestos workers.

Epidemiological studies of cohorts with asbestos-related diseases – asbestosis and benign pleural disease – have not found increased mortality for cancer of the stomach (Germani *et al.*, 1999; Karjalainen *et al.*, 1999; Szeszenia-Dabrowska *et al.*, 2002).

(b) Case–control studies

Case–control studies exploring the relationship between asbestos exposure and cancer of the stomach yield inconsistent results. The Working Group reviewed five case–control studies. Notable findings are these:

A study from Poland (Krstev *et al.*, 2005) found an OR for cancer of the stomach of 1.5 (95%CI: 0.9–2.4) for workers ever exposed to asbestos, and of 1.2 (95%CI: 0.6–2.3) for workers with 10 or more years of exposure to asbestos.

The largest case–control study to examine the association between asbestos and cancer of the stomach (Cocco *et al.*, 1994) reported an odds ratio of 0.7 (95%CI: 0.5–1.1) for workers ever exposed to asbestos, and of 1.4 (95%CI: 0.6–3.0) for those with 21+ years of exposure to asbestos.

The most strongly positive case–control study linking asbestos to cancer of the stomach is the case–control study, cited above, nested within the Western Australia mining cohort (Reid *et al.*, 2004).

(c) Meta-analyses

Several meta-analyses have been undertaken of the association between asbestos exposure and cancer of the stomach.

A meta-analysis by Frumkin & Berlin (1988) stratified studies according to SMR for lung cancer and also according to percentage of deaths due to mesothelioma. Frumkin & Berlin found in cohorts where the SMR for lung cancer was < 2.00 that the SMR for cancer of the stomach was 0.91 (95%CI: 0.71–1.16). By contrast, when the SMR for lung cancer was > 2.00, the SMR for cancer of the stomach increased to 1.34 (95%CI: 1.07–1.67).

Gamble (2008) reported that point estimates for cancer of the stomach mortality tended towards 1.0 when the excess risk for lung cancer were less than 4-fold, but "tended to be somewhat elevated when lung cancer relative risks were 4-fold or greater." Gamble observed further that "combined relative risks for cancer of the stomach stratified by lung cancer categories showed a suggestive trend, with a significant deficit (0.80) when lung cancer SMRs were <1.0 that increased monotonically to a significant 1.43-fold excess in the studies with lung cancer SMRs > 3.0." Gamble observed no trend for increasing SMR for cancer of the stomach with increasing percentage of deaths from mesothelioma (Gamble, 2008).

The IOM (2006) conducted a meta-analysis of 42 cohort studies examining the association between asbestos exposure and cancer of the stomach. The IOM noted that the "majority of cohort relative risk estimates for cancer of the stomach exceed the null value (1.0), indicating excesses, although estimates varied considerably in strength." In cohorts that compared "any" versus no exposure, the summary relative risk was 1.17 (95%CI: 1.07–1.28). The IOM notes that with respect to dose–response, the summary estimates were stable. Thus in the cohorts that compared "high" versus no exposure, the lower bound summary relative risk was 1.31 (95%CI: 0.97–1.76), and the higher bound summary relative risk, 1.33 (95%CI: 0.98–1.79).

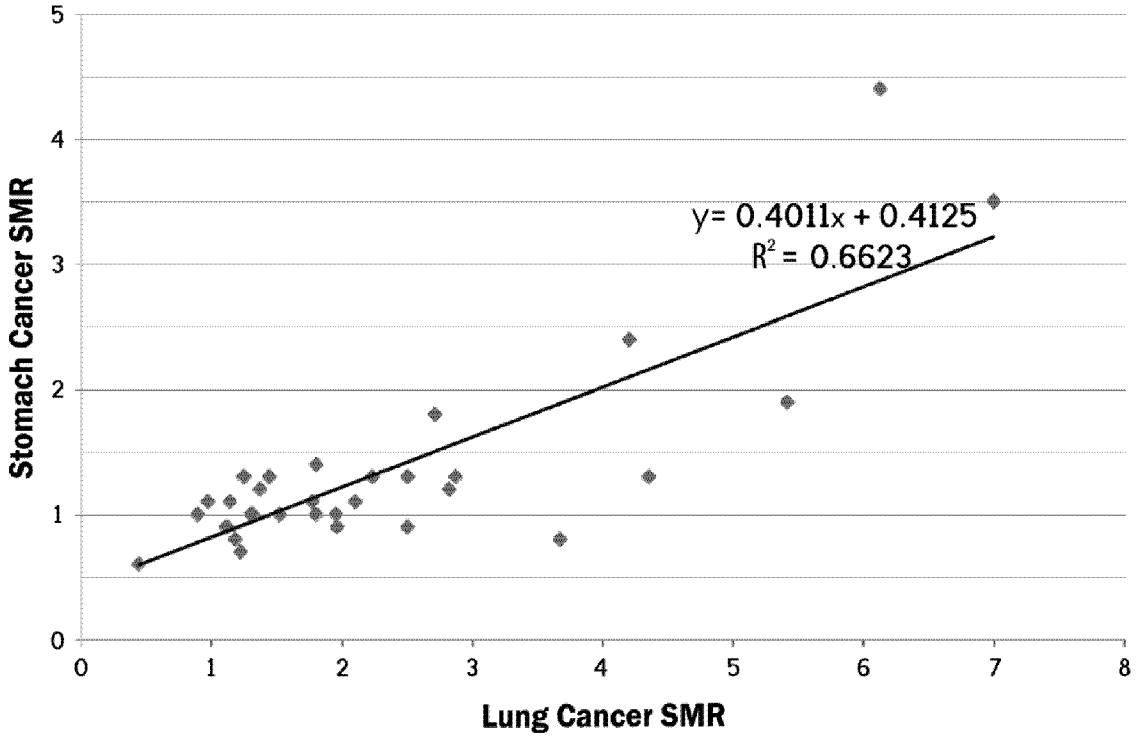
The IOM conducted a meta-analysis of the five case–control studies resulting in a combined relative risk of 1.11 (95%CI: 0.76–1.64). The summary odds ratio increased when only extreme exposure was considered (OR, 1.42; 95%CI: 0.92–2.20)

The Working Group developed a scatter plot comparing SMRs for lung cancer with SMRs for cancer of the stomach in the same cohorts. A positive trend was observed between the two, and the correlation coefficient (r2) = 0.66, see Fig. 2.1.

(i) Asbestos in drinking-water and cancer of the stomach

Ecological correlational studies conducted from the 1960s into the early 1980s suggested an association between asbestos in drinking-water and cancer of the stomach. These studies correlated population exposure to asbestos in water supplies with population cancer rates. Levy *et al.* (1976) reported an excess in cancer of the stomach among persons in Duluth, MN, USA exposed to taconite asbestos in drinking-water. Wigle (1977) saw an excess of male cancer of the stomach among some exposed to asbestos in drinking-water in Quebec. Conforti *et al.* (1981)

Fig 2.1 Stomach & lung cancer correlation in asbestos cohorts



Compiled by the Working Group

saw a similar association in the San Francisco Bay area, USA. Polissar *et al.* (1982) examined cancer incidence and mortality among residents of the Puget Sound area, USA, in relation to asbestos in regional drinking-water. They observed no association between asbestos exposure and cancer of the stomach. A similarly negative study was observed in a study conducted in Woodstock, NY, USA (Howe *et al.*, 1989).

Kjærheim *et al.* (2005) examined cancer of the stomach incidence in Norwegian light-house keepers exposed to asbestos in drinking-water. They found an SIR for cancer of the stomach in the entire cohort of 1.6 (95%CI: 1.0–2.3). In the subcohort with "definite" exposure to asbestos, the SIR was 2.5 (95%CI: 0.9–5.5). In those members of the definite exposure subcohort followed for 20+ years, the SIR was 1.7 (95%CI: 1.1–2.7).

Cantor (1997) conducted a systematic review of the epidemiological literature on exposure to asbestos in drinking-water and cancer of the stomach, and concluded that the available data were inadequate to evaluate the cancer risk of asbestos in drinking-water.

Marsh (1983) conducted a critical analysis of 13 epidemiological studies of asbestos and drinking-water conducted in the USA and Canada, and found no consistent pattern of association.

2.4.5 Cancer of the colorectum

The Working Group examined data from 41 occupational cohorts and 13 case–control studies that reported data on associations between asbestos exposure and cancer of the colon and rectum (See Table 2.7 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-06-Table2.7.pdf). The Working Group made the decision to combine information on these two sites, although a few comments in several places in the text about the two sites considered separately have also been made.

(a) Cohort studies

An association between occupational exposure to asbestos and cancer of the colorectum was first reported in 1964 by Selikoff *et al.* in a cohort of 632 male insulation workers in New York and New Jersey, USA (Selikoff *et al.*, 1964). Further analysis of this cohort found a positive relationship between duration of work with asbestos and risk of cancer of the colorectum, in that the SMR increased from 0.00 (95%CI: 0.00–18.45) in workers with < 20 years exposure, to 3.68 (95%CI: 1.48–7.59) among workers with 20–35 years' exposure, and to 2.58 (95%CI: 1.48–4.19) among workers with the longest duration of exposure, > 35 years (Selikoff & Hammond, 1979).

Selikoff *et al.* (1967), in a second report, found an association between occupational exposure to asbestos and cancer of the colorectum in a population of 17800 asbestos insulators across the USA and Canada (SMR, 1.37; 95%CI: 1.14–1.64).

Seidman *et al.* (1986) reported an elevated mortality from cancer of the colorectum in a population of 820 male factory workers in Paterson, NJ, USA, exposed to amosite asbestos (SMR, 2.77; 95%CI: 1.16–2.80). They noted that cancer of the colorectum in asbestos workers tended to be a disease of long latency; they reported that the ratio of observed to expected deaths increased with increasing interval since initial exposure to asbestos.

McDonald *et al.* (1980) reported an overall SMR for cancer of the colorectum of only 0.78 in a study of 10939 men and 440 women workers employed as asbestos miners and millers in Quebec with predominant exposure to chrysotile asbestos. Additionally, however, McDonald *et al.* reported a "clear trend for SMRs to be higher, the heavier the exposure." Thus with increasing levels of cumulative occupational exposure to asbestos dust, relative risks for cancer of the colorectum increased in this cohort from 1.00 in workers with less than 30 mpcf–y cumulative exposure, to 0.93 in workers with 30–300 mpcf–y, to 1.96 in workers with 300–1000 mpcf–y, and then in the group with heaviest exposure, > 1000 mpcf–y, to 5.26.

Albin *et al.* (1990) found an overall SMR for cancer of the colorectum of only 1.5 (95%CI: 0.7–3.0) in a cohort of 1465 asbestos-cement workers in Sweden. A positive association between asbestos exposure and cancer of the colorectum was reported, but when cancer of the colorectum mortality was examined by individual cumulative exposure to asbestos, measured as fibre–years/mL, the SMR was 1.3 (95%CI: 0.5–2.9) for those workers with cumulative exposure of < 15 fibre–years/mL; for those with cumulative exposure of 15–39 fibre–years/mL, the SMR was 1.1(95%CI: 0.3–3.9); and for those workers in highest exposure category with > 40 fibre–years/mL, the SMR for cancer of the colorectum was 3.4 (95%CI: 1.2–9.5). Diagnosis in all but one of the cancers in the highest exposure category was verified by pathological review, and no case of certified or probable mesothelioma was found. The trend towards increasing mortality from cancer of the colorectum with increasing cumulative exposure to asbestos was statistically significant ($P = 0.04$). A similar trend was seen for cancer of the colorectum morbidity.

Excess mortality from colon cancer was observed in a heavily exposed cohort of over

5000 workers in the east end of London, who had produced asbestos insulation board and were followed for 30+ years (Berry *et al.*, 2000). The overall SMR for colon cancer in this cohort was 1.83 (95%CI: 1.20–2.66). There was evidence for a positive dose–response relationship, in that excess mortality from colon cancer was confined to men who had worked as laggers or had been severely exposed for more than 2 years. This positive trend was statistically significant ($P = 0.017$).

In a cohort comprised of family members of men who had been employed in an asbestos-cement factory in Casale Monferrato, Italy, Ferrante *et al.* (2007) examined cancer mortality. Among women with domestic exposure to asbestos, 21 deaths from cancer of the "intestine and rectum" versus 16.0 expected (SMR, 1.31; 95%CI: 0.81–2.0) were observed. For cancer of the rectum, ten deaths versus five expected (SMR, 2.00; 95%CI: 0.96–3.69) were observed.

Several other cohort studies of occupationally exposed populations in a variety of industries have also found evidence for an association between asbestos exposure and cancer of the colorectum (Puntoni *et al.*, 1979: Hilt *et al.*, 1985; Jakobsson *et al.*, 1994; Raffn *et al.*, 1996; Szeszenia-Dabrowska *et al.*, 1998; Smailyte *et al.*, 2004).

Jakobsson *et al.* (1994) examined colon cancer by anatomical location in asbestos-cement workers, and observed an increased incidence of malignancy in the right side of the colon, but not in the left side.

A report on incidence of cancer of the colorectum from the Beta-Carotene and Retinol Efficacy Trial (CARET) found a relative risk of 1.36 (95%CI: 0.96–1.93) among 3987 heavy smoker participants occupationally exposed to asbestos as compared to smoker participants not exposed to asbestos (Aliyu *et al.*, 2005). Of note was the finding that the relative risk for cancer of the colorectum was 1.54 (95%CI: 0.99–2.40) among participants with asbestos-induced pleural plaques. The investigators interpreted the presence of pleural plaques as a marker for heavy individual exposure to asbestos. Risk for cancer of the colorectum also increased with worsening pulmonary asbestosis ($P = 0.03$ for trend). It was reported that a "dose–response trend based on years of asbestos exposure was less evident".

(b) Case–control studies

Evidence from case–control studies of asbestos and cancer of the colorectum is in general less strong than the evidence from the cohort studies. However, case–control studies from the Nordic countries and the USA have, however, reported significant increases in asbestos-associated odds ratios in occupationally exposed poulations (Fredriksson *et al.*, 1989; Gerhardsson de Verdier *et al.*, 1992; Vineis *et al.*, 1993; Kang *et al.*, 1997; Goldberg *et al.*, 2001).

Consideration of latency since first exposure appears to be an important factor in assessing these studies. Thus, Gerhardsson de Verdier *et al.* (1992) examined incidence of cancer of the colorectum by interval since first occupational exposure and observed "for subjects exposed to asbestos, the risks were highest when the latency period was more than 39 years." Gerhardsson de Verdier *et al.* observed further that the relative risk for cancer of the right colon was 2.6 (95%CI: 1.2–5.9) among workers exposed to asbestos, and that for malignancy of the left colon, only 0.5 (95%CI: 0.1–1.9).

Other cohort and case–control studies have not found evidence for an association between asbestos exposure and cancer of the colorectum (Gardner *et al.*, 1986; Hodgson & Jones, 1986; Garabrant *et al.*, 1992; Dement *et al.*, 1994; Demers *et al.*, 1994; Tulchinsky *et al.*, 1999; Hein *et al.*, 2007; Loomis *et al.*, 2009).

(c) Meta-analyses

Some of these meta-analyses have stratified studies according to the standardized mortality ratio for lung cancer or the percentage of deaths due to mesothelioma:

Morgan *et al.* (1985) found a summary standardized mortality ratio for cancer of the colorectum of 1.13 (95%CI: 0.97–1.30). This was reduced to 1.03 (95%CI: 0.88–1.21) after deleting cases in which the diagnosis of cancer of the colorectum was based on "best evidence" (pathological review) rather than death certificate data.

Frumkin & Berlin (1988) found in cohorts where the standardized mortality ratio for lung cancer was < 2.00 that the standardized mortality ratio for cancer of the colorectum was 0.86 (95%CI: 0.69–1.09). By contrast, when the standardized mortality ratio for lung cancer was > 2.00, the standardized mortality ratio for cancer of the colorectum increased to 1.61 (95%CI: 1.34–1.93).

Homa *et al.* (1994) found an elevated summary standardized mortality ratio for cancer of the colorectum in cohorts exposed to serpentine asbestos that had an standardized mortality ratio for lung cancer > 2.00 (summary standardized mortality ratio for cancer of the colorectum, 1.73; 95%CI: 0.83–3.63), and also in cohorts exposed to a mix of amphibole and serpentine asbestos that had a standardized mortality ratio for lung cancer > 2.00 (summary standardized mortality ratio for cancer of the colorectum, 1.48; 95%CI: 1.24–1.78). Among cohorts exposed to amphibole asbestos, the standardized mortality ratio for cancer of the colorectum was elevated regardless of the standardized mortality ratio for lung cancer. Homa *et al.* (1994) saw similar trends between standardized mortality ratio for cancer of the colorectum and percentage of deaths from mesothelioma.

Gamble (2008) reported that there was "tendency for CRC [cancer of the colorectum] risk ratios to be elevated when lung cancer risk ratios are >4" and further noted a significantly elevated standardized mortality ratio of 1.60 (95%CI: 1.29–2.00) for cancer of the colorectum when the standardized mortality ratio for lung cancer exceeds 3.00. Gamble (2008) observed no trend in cancer of the colorectum mortality with increasing percentage of deaths due to mesothelioma. Gamble saw no association between asbestos exposure and rectal cancer.

The IOM (2006) conducted a meta-analysis of cohort studies examining the association between asbestos exposure and cancer of the colorectum. In studies that compared "any" versus no exposure, the summary relative risk was 1.15 (95%CI: 1.01–1.31). For studies comparing "high" versus no exposure, the lower-bound summary relative risk was 1.24 (95%CI: 0.91–1.69), and the upper-bound summary relative risk, 1.38 (95%CI: 1.14–1.67).

The IOM also conducted a meta-analysis of the published case–control studies. Overall, 13 studies comparing "any" versus no exposure yielded a summary relative risk of 1.16 (95%CI: 0.90–1.49).

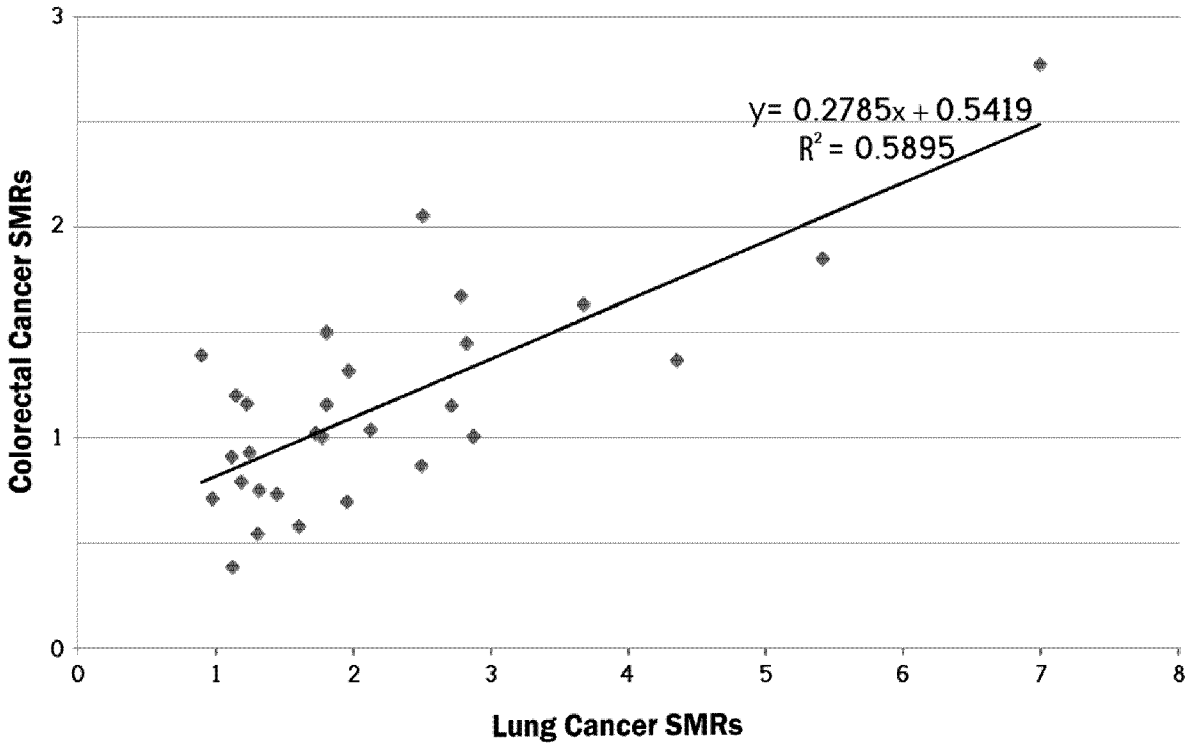
The *IARC Monograph* 100C Working Group developed a scatter plot comparing standardized mortality ratios for lung cancer with standardized mortality ratios for cancer of the colorectum in the same cohorts. The trend was positive with a correlation coefficient (r2) of 0.59, see Fig. 2.2.

(i) Asbestos in drinking-water and cancer of the colorectum

Ecological correlational studies conducted from the 1960s into the early 1980s suggested an association between asbestos in drinking-water and cancer of the colon. These studies correlated population exposure to asbestos in water supplies with population cancer rates. Polissar *et al.* (1982) examined cancer incidence and mortality among residents of the Puget Sound area, USA, in relation to asbestos in regional drinking-water. No association between asbestos exposure and colon cancer was observed. A similarly negative study was observed in a study conducted in Woodstock, NY, USA (Howe *et al.*, 1989).

Kjærheim *et al.* (2005) examined colon cancer incidence in Norwegian light-house keepers exposed to asbestos in drinking-water. The standardized incidence ratio for colon cancer in

Fig 2.2 Colorectal & lung cancer correlation in asbestos cohorts



Compiled by the Working Group

the entire cohort was 1.5 (95%CI: 0.9–2.2). In the subcohort with "definite" exposure to asbestos, the standardized incidence ratio was 0.8 (95%CI: 0.1–2.9). In those members of the definite exposure subcohort followed for 20+ years, the standardized incidence ratio was 1.6 (95%CI: 1.0–2.5).

Cantor (1997) conducted a systematic review of the epidemiological literature on exposure to asbestos in drinking-water and colon cancer and concluded that the data were inadequate to evaluate colon cancer risk of asbestos in drinking-water.

Marsh (1983) conducted a critical analysis of 13 epidemiological studies of asbestos and drinking-water conducted in the USA and Canada and found no consistent pattern of association.

2.4.6 Cancer of the ovary

The published literature examining the association between asbestos exposure and cancer of the ovaries is relatively sparse, because the workforce occupationally exposed to asbestos in such occupations as mining, milling shipyard work, construction and asbestos insulation work has been predominantly male. An examination of the association between asbestos and ovarian cancer was not undertaken by the IOM (2006).

See Table 2.8 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-06-Table2.8.pdf.

(a) Cohort studies

The Working Group examined 11 cohort studies that examined the association between asbestos exposure and ovarian cancer in 13 populations, ten with occupational exposure to asbestos and three with community-based or residential exposure.

Acheson *et al.* (1982) examined a cohort in the United Kingdom consisting of two groups of women in separate factories ($n = 1327$), employed in the manufacture of asbestos-containing gas masks before and during World War II. One factory had used crocidolite asbestos, and the other had used chrysotile. Among 757 women in the plant that used crocidolite, 12 deaths from ovarian cancer were observed versus. 4.4 expected (SMR, 2.75; 95%CI: 1.42–4.81). Among 570 women in the plant that used chrysotile asbestos, five deaths were observed for ovarian cancer versus 3.4 expected (SMR, 1.48; 95%CI: 0.48–3.44).

Wignall & Fox (1982) conducted a 30-year, follow-up mortality study of a population of 500 women in the United Kingdom employed in the manufacture of asbestos-containing gas masks before and during World War II. The type of asbestos used was crocidolite. A total of six deaths from ovarian cancer were obserevd versus. 2.8 expected (SMR, 2.13). When the cohort was subdivided according to degree of exposure to asbestos, the highest mortality from ovarian cancer was found among the subgroup definitely exposed to asbestos from the early 1940s (SMR, 14.81; $P < 0.01$). Overall five deaths from ovarian cancer were found among women definitely exposed to asbestos (versus 0.63 expected), whereas none were found among women definitely not exposed to asbestos (versus 0.40 expected).

To address potential misclassification of some deaths in this cohort recorded on death certificates as ovarian cancer as opposed to peritoneal mesothelioma, Wignall & Fox (1982) conducted a histopathological review of the cases cases of diagnosed ovarian cancer for which tissue material was available. One of these three cases was found to be peritoneal mesothelioma, while the diagnosis of ovarian cancer was sustained in the other two cases.

In a cohort study of 700 women factory workers employed in an asbestos-board insulation manufacturing company in the east end of London and followed for 30+ years, Berry *et al.* (2000) observed nine deaths from ovarian cancer versus 3.56 expected (SMR, 2.53; 95%CI: 1.16–4.80) (Berry *et al.*, 2000), with evidence for a positive exposure–response relationship. Among women with low-to-moderate exposure to asbestos, two deaths were observed versus 0.54 expected; in the subset with "severe" asbestos exposure of < 2 years' duration, two deaths were observed versus 2.12 expected. (SMR, 0.94); and among women with severe exposure of > 2 years' duration, five deaths from ovarian cancer were observed versus 0.90 expected (SMR, 5.35).

An assessment was performed of the significance of the positive exposure–response trend ($P = 0.18$). To address the potential misclassification of some deaths in this cohort having been recorded as ovarian cancer as opposed to peritoneal mesothelioma, Newhouse *et al.* (1972) conducted a histopathological review of the four deaths that by 1972 had been recorded as due to ovarian cancer; three of the four had occurred in women with severe and prolonged exposure to asbestos. Histological material was available for two of these cases. In both, the diagnosis of ovarian cancer was confirmed.

Reid *et al.* (2008) reported on cancer mortality in a cohort of 2552 women and girls who lived in the crocidolite asbestos mining town of Wittenoom in Western Australia during 1943–92, who were not involved in asbestos

mining and milling. Environmental contamination of the town with asbestos dust is reported to have been extensive. The women's exposure was environmental and not occupational. There were nine deaths from ovarian cancer in this cohort (SMR, 1.26; 95%CI: 0.58–2.40).

Reid *et al.* (2009) conducted a cancer incidence study in the same cohort of 2552 women and girls in Western Australia with environmental exposure to crocidolite asbestos. Additionally, they examined cancer incidence in 416 women who had worked in various capacities in the Wittenoom crocidolite asbestos mines and mills. Among community residents, ten incident cases of ovarian cancer were observed (SIR, 1.18; 95%CI: 0.45–1.91). Among women workers employed in the asbestos factory, one case of ovarian cancer was observed (SIR, 0.49; 95%CI: 0.01–2.74).

To address the possibility that some diagnosed cases of ovarian cancer in this cohort might in fact have been cases of peritoneal mesothelioma, Reid *et al.* (2009) examined pathological material from nine of their cases. The diagnosis of ovarian cancer was sustained in every case.

Pira *et al.* (2005) conducted a cohort study of 1077 women employed for at least one month during 1946–84 in an asbestos-textile factory in Italy, and followed up to 1996. A variety of types of asbestos were used in the factory, including crocidolite. A non-significantly increased standardized mortality ratio of 2.61 was observed for cancer of the ovary, based on five deaths. Among women in this cohort with ≥ 10 years of employment with asbestos, the standardized mortality ratio for ovarian cancer was 5.73, based on three deaths. Among women with ≥ 35 years since first employment, the standardized mortality ratio for ovarian cancer was 5.37, based on two deaths. This cohort was heavily exposed to asbestos, as supported by a standardized mortality ratio for lung cancer among women of 5.95, and by the occurrence of 19 deaths from mesothelioma (12%) among 168 total deaths in women.

Magnani *et al.* (2008) examined cancer mortality among a cohort of former workers at a now closed asbestos-cement factory in Casale Monferrato, Italy. A mix of crocidolite and chrysotile asbestos was used in this factory. Among women workers, there was an excess of ovarian cancers: nine observed versus 4.0 expected (SMR, 2.27; $P < 0.05$). Among women workers with 30 or more years exposure, the standardized mortality ratio for ovarian cancer was 2.97. Bertolotti *et al.* (2008) described the same findings in the same cohort [in Italian].

Ferrante *et al.* (2007) examined cancer mortality in a cohort consisting of family members of men who had been employed in the asbestos-cement factory in Casale Monferrato, Italy, described in the preceding paragraph. Exposure was to a mix of crocidolite and chrysotile. Among women with domestic exposure to asbestos, 11 deaths from ovarian cancer were observed versus 7.7 expected (SMR, 1.42; 95%CI: 0.71–2.54).

Germani *et al.* (1999) examined mortality from ovarian cancer in a cohort of 631 women workers in Italy who had been compensated for asbestosis. The type of fibre to which the women were exposed was not specified. In the total cohort, there were nine deaths from ovarian cancer (SMR, 4.77; 95%CI: 2.18–9.06). In the subset of women from the asbestos-textile industry, there were four deaths from ovarian cancer (SMR, 5.26; 95%CI: 1.43–13.47). In the subcohort from the asbestos cement industry, there were five deaths from ovarian cancer (SMR = 5.40; 95%CI: 1.75 – 12.61).

Rösler *et al.* (1994) examined cancer mortality in a cohort of 616 women workers in Germany who had been occupationally exposed to asbestos. Proportionate mortality was computed according to cause of death. A total of 95% of the asbestos used in Germany at this time was chrysotile, but the authors state that "admixture of crocidolite cannot be excluded, particularly in the manufacture of asbestos textile." Two deaths

from ovarian cancer were observed versus 1.8 expected (SMR, 1.09; 95%CI: 0.13–3.95).

(i) Population-based cohort studies

Vasama-Neuvonen *et al.* (1999) conducted a case–control study of ovarian cancer of occupational exposures in Finland. The asbestos fibre type was not specified and the standardized incidence ratio was 1.30 (95%CI: 0.9–1.80) between ovarian cancer and exposure to "high levels of asbestos."

Pukkala *et al.* (2009) examined the incidence of ovarian cancer among women employed in various occupational categories in Nordic countries (Denmark, Finland, Iceland, Norway, and Sweden). Among the groups examined were plumbers, a group with known occupational exposure to asbestos. Fibre type was not specified. A total of four ovarian cancers were observed in these women plumbers. The standardized incidence ratio was 3.33 (95%CI: 0.91–8.52)

(b) Case–control studies

Langseth & Kjærheim (2004) conducted a nested case–control study to examine the association between asbestos exposure and ovarian cancer within a cohort of female pulp and paper workers in Norway that had previously been found to have excess mortality from ovarian cancer (37 ovarian cancers observed versus 24 expected; SIR, 1.50; 95%CI: 1.07–2.09). The asbestos fibre type was not specified. In the case–control study, the odds ratio for occupational exposure to asbestos, based on 46 cases of ovarian cancer, was 2.02 (95%CI: 0.72–5.66).

2.5 Synthesis

The Working Group noted that a causal association between exposure to asbestos and cancer of the larynx was clearly established, based on the fairly consistent findings of both the occupational cohort studies as well as the case-controlcase–control studies, plus the evidence for positive exposure–response relationships between cumulative asbestos exposure and laryngeal cancer-cancer of the larynx reported in several of the well-conducted cohort studies. This conclusion was further supported by the meta-analyses of 29 cohort studies encompassing 35 populations and of 15 case-controlcase–control studies of asbestos exposure and laryngeal cancercancer of the larynx undertaken by the IOM (2006). However, there is insufficient information in the published literature to discern whether any differences exist among asbestos fibre types in their ability to cause laryngeal cancercancer of the larynx.

The Working Group noted that a causal association between exposure to asbestos and cancer of the ovary was clearly established, based on five strongly positive cohort mortality studies of women with heavy occupational exposure to asbestos (Acheson *et al.*, 1982; Wignall & Fox, 1982; Germani *et al.*, 1999; Berry *et al.*, 2000; Magnani *et al.*, 2008). The conclusion received additional support from studies showing that women and girls with environmental, but not occupational exposure to asbestos (Ferrante *et al.*, 2007; Reid *et al.*, 2008, 2009) had positive, though non-significant, increases in both ovarian cancer incidence and mortality.

The Working Group carefully considered the possibility that cases of peritoneal mesothelioma may have been misdiagnosed as ovarian cancer, and that these contributed to observed excesses. Contravening that possibility is the finding that three of the studies cited here specifically examined the possibility that there were misdiagnosed cases of peritoneal mesothelioma, and all failed to find sufficient numbers of misclassified cases. The Working Group noted that the possibility of diagnostic misclassification had probably diminished in recent years because of the development of new immunohistochemical diagnostic techniques.

The conclusion of the Working Group received modest support from the findings of

non-significant associations between asbestos exposure and ovarian cancer in two case–control studies (Vasama-Neuvonen *et al.*, 1999; Langseth & Kjærheim, 2004).

And lastly, the finding is consistent with laboratory studies documenting that asbestos can accumulate in the ovaries of women with household exposure to asbestos (Heller *et al.*, 1996) or with occupational exposure to asbestos (Langseth *et al.*, 2007).

The study by Heller *et al.* (1996) was a histopathological study of ovaries from 13 women who had household contact with men who had documented exposure to asbestos, and of 17 women who gave no history of potential for asbestos exposure. The study found "significant asbestos fibre burdens" in the ovaries of nine (60.2%) of the exposed women and in only six (35%) of the unexposed women. Three of the exposed women had asbestos fibre counts in ovarian tissue of over 1 million fibres per gram (wet weight). By contrast, only one of the 17 women without household exposure had counts in that range.

The study by Langseth *et al.* (2007) found approximately 3–4 × 105 asbestos fibres per gram (net weight) in normal ovarian tissue taken from 2/46 patients with ovarian adenocarcinoma. It is unclear how many of these fibres were verified as asbestos because it is stated in the publication that three chrysotile and one crocidolite asbestos fibres were identified in Case 1, and two anthophyllite and one chrysotile fibre were identified in Case 2. This small number of confirmed asbestos fibres in only two of the patients could be due to sample contamination. Technical caveats associated with quantification of asbestos fibre tissue burdens are discussed in Section 4 of this *Monograph* and in IOM (2006).

Further discussion of the biological plausibility of an association between asbestos exposure and ovarian cancer is to be found in Section 4 of this *Monograph*.

The Working Group noted a positive association between exposure to abestos and cancer of the pharynx, based on the fairly consistent positive findings in a series of well conducted cohort studies of populations occupationally exposed to asbestos (Selikoff & Seidman, 1991; Sluis-Cremer *et al.*, 1992; Reid *et al.*, 2004; Pira *et al.*, 2005) as well as on the positive findings of three case–control studies (Zheng *et al.*, 1992; Marchand *et al.*, 2000; Berrino *et al.*, 2003). This conclusion was further supported by the findings of the meta-analysis conducted by the IOM. While tobacco smoking and alcohol consumption are clearly the dominant risk factors for cancer of the pharynx in industrialized countries, these associations between cancer of the pharynx and asbestos remained evident in several studies when tobacco and alcohol exposures were considered. The Working Group observed that the strongest associations between asbestos exposure and cancer of the pharynx were seen in studies that specifically examined cancer of the hypopharynx, the portion of the pharynx that is located closest to the larynx. However, there is insufficient information in the published literature to discern whether there are any differences among asbestos fibre types in their ability to cause cancer of the pharynx.

The Working Group noted a positive association between exposure to abestos and cancer of the stomach, based on the positive associations between asbestos exposure and death from stomach cancer observed in several of the cohort studies with heaviest asbestos exposure (Selikoff *et al.*, 1964; Enterline *et al.*, 1987; Raffn *et al.*, 1989; Liddell *et al.*, 1997; Musk *et al.*, 2008). The conclusion was further supported by the positive dose–response relationships observed between cumulative asbestos exposure and stomach cancer mortality in several cohort studies (Selikoff & Hammond., 1979; Zhang & Wang, 1984; Liddell *et al.*, 1997; Pang *et al.*, 1997). It was supported by the results of two large and well performed meta-analyses (Frumkin & Berlin, 1988; Gamble, 2008). It received borderline support from the IOM meta-analysis of cohort

studies, and also from the IOM meta-analysis of case–control studies, which show an especially strong relationship when only extreme exposures are considered. It was supported by the comparison developed by the Working Group between standardized incidence ratios for lung cancer and stomach cancer.

Positive associations between asbestos exposure and stomach cancer and positive dose–response relationships are most likely to be seen in studies of populations with prolonged heavy exposure to asbestos that had long-term follow-up, and that incorporated high-quality assessments of exposure. The less detailed assessments of exposure found in many of the published studies would have tended to bias study results towards the null, and thus impede recognition of an association between asbestos exposure and stomach cancer, even if such an association were truly present.

[The Working Group noted that heavy occupational exposure to dust, as had likely occurred in the case of the Quebec asbestos cohort, could have been an effect modifier. Low socioeconomic status is also a potential confounder.]

However, there was insufficient information in the published literature to discern whether any differences exist among asbestos fibre types in their ability to cause stomach cancer. In the study by Liddell *et al.* (1997) exposure was to virtually pure chrysotile asbestos, in the study by Musk *et al.* (2008) the exposure was predominantly to crocidolite, and in most of the other published studies that observed positive associations, populations were exposed to mixtures of different asbestos fibres.

The Working Group noted a positive association between exposure to abestos and cancer of the colorectum, based on the fairly consistent findings of the occupational cohort studies, plus the evidence for positive exposure–response relationships between cumulative asbestos exposure and cancer of the colorectum consistently reported in the more detailed cohort studies (McDonald *et al.*, 1980; Albin *et al.*, 1990; Berry *et al.*, 2000; Aliyu *et al.*, 2005). The conclusion was further supported by the results of four large and well performed meta-analyses (Frumkin & Berlin 1988; Homa *et al.*, 1994; IOM, 2006; Gamble, 2008).

Positive exposure–response relationships between asbestos exposure and cancer of the colorectum appear most likely to be seen in studies of populations with prolonged heavy exposure to asbestos that had long-term follow-up, and that incorporated high-quality assessments of exposure. The less detailed assessments of exposure found in many of the published studies would have tended to bias study results towards the null, and thus impede recognition of an association between asbestos exposure and cancer of the colorectum, even if such an association were truly present.

The apparently non-positive findings of several the case–control studies are not a deterrent to this conclusion. The majority of these case–control studies incorporated relatively little information on levels of asbestos exposure; indeed, most of them considered exposure as simply a dichotomous yes/no variable. Some of the case–control studies also may be compromised by inadequate duration of follow-up. Thus, the Garabrant study (Garabrant *et al.*, 1992) may be subject to the criticism, offered by Gerhardsson de Verdier *et al.* (1992) that "the highest duration of exposure…was 'at least 15 years,' a period that may be too short to detect an elevated risk."

There is some suggestion in the literature that the association between asbestos might be stronger for colon cancer than for rectal cancer. This view is supported by the meta-analysis of Gamble (2008) which found a positive dose–response relationship for cancer of the colorectum taken together, but not for rectal cancer. It is supported also by the study of Jakobsson *et al.* (1994), which found excess of cancer of the right colon in asbestos-exposed workers, but not of the left colon.

However, there was insufficient information in the published literature to discern whether any differences exist among asbestos fibre types in their ability to cause cancer of the colorectum. It is of note in the study by McDonald *et al.* (1980) that exposure was to virtually pure chrysotile asbestos, whereas in most of the other studies cited above, populations were exposed to mixtures of different asbestos fibres.

3. Cancer in Experimental Animals

3.1 Introduction

Asbestos is a collective name for six different types of fibres: chrysotile, crocidolite, amosite, anthophyllite, tremolite, actinolite (see Section 1). Dusts from various deposits of the same type of asbestos can cause variations in the severity of the effects observed. Erionite is a fibrous zeolite found in Central Anatolia (Turkey), and Oregon (USA) (see Section 1 of the *Monograph* on Erionite). Talc is a hydrated magnesium silicate, and talc ore may contain several other minerals including anthophyllite, tremolite, calcite, dolomite, magnesite, antigorite, quartz, pyrophyllite micas, or chlorites (see Section 1).

The definition of pathogenic fibre properties as "sufficiently long, thin, and durable" is the subject of much debate, as are the differences between the exposure–response relationships or retained dose–response relationships of asbestos fibres in man and in rats, and the potential differences in the carcinogenicity of chrysotile compared to the various amphibole asbestos types. One of the reasons for a potential difference is a difference in the biopersistence between the two asbestos groups mentioned. The biopersistence is higher in the amphibole group (Hesterberg *et al.*, 1996, 1998a, b). The rat is the main test model for fibre-induced diseases. As the removal of asbestos fibres due to biosolubility is slow compared to the lifetime of rats and hamsters, experiments with this model may not be appropriate in predicting results of risk in humans (Berry, 1999).

Critical fibre dimensions to be used in toxicology and occupational regulations were discussed by the Working Group. It is generally agreed that the carcinogenic potency of a fibre increases with fibre length. Apart from the ongoing scientific view, standards of regulated fibres, with few exceptions, are based on the WHO fibre definition: aspect ratio ≥ 3: 1, length ≥ 5 μm, diameter ≤ 3 μm.

The tested materials (asbestos and erionite) are not presented in separate tables as in many cases they were tested in parallel experiments. The reason to split the inhalation studies into two tables (Table 3.1; Table 3.2) is that in many studies, various asbestos fibres were used as positive control in studies in which man-made fibres were tested (Table 3.2). In these latter studies, normally only one asbestos concentration was used. As for intrapleural and intraperitoneal studies, Table 3.4 is separate from Table 3.5 because the studies of Stanton *et al.* (1981) (see Table 3.5) included many fibre types – which also included fibres not to be reviewed here – and was designed to investigate the effect of fibre length and fibre type on mesothelioma induction.

A general evaluation on the type of fibre application in animal studies and an evaluation of some of the asbestos studies listed in Tables 3.1–3.5 can be found in Pott (1993) and IARC (2002).

3.2 Inhalation exposure

Table 3.1 and Table 3.2 give an overview of the numerous inhalation experiments on asbestos, and a few experiments on erionite. Some of these are described more extensively below.

Bronchial carcinomas and pleural mesotheliomas have been observed in rats after exposure to chrysotile, crocidolite, amosite, anthophyllite, and tremolite fibres. In these studies, there was no consistent increase in

tumour incidence at other sites. [The Working Group noted that in many studies, no complete histopathology was done.] All relatively short UICC asbestos preparations showed chronic effects in lung (based on fibre lenghts > 5 µm in the dust chamber) for fibres quantitatively roughly the same.

One of the first inhalation study with asbestos in rats that showed exposure–response relationships is the experiment of Wagner *et al.* (1974). Wistar rats were exposed to 10–15 mg/m^3 of one of the five UICC standard asbestos samples for 7 hours per day, mostly 5 days per week. The duration of exposure lasted from one day to 24 months. According to the reported data, in the group exposed to crocidolite for one day, lung tumours and one mesothelioma were found in 7/43 rats (16%). The corresponding exposure to chrysotile A (from Canada) resulted in lung tumours in 5/45 rats; for amosite 4/45 rats developed lung tumours and one mesothelioma. Three months of exposure to the five UICC standard asbestos samples resulted in the following thoracic tumour (mainly of the lung) incidences: chrysotile A, 44%;chrysotile B (from Zimbabwe), 53%; crocidolite, 42%; amosite, 27%; anthophyllite, 16%. Further results are listed in Table 3.1. In the 126 control rats, seven animals were also found to have lung tumours (Table 3.3). This high spontaneous lung tumour rate is a unique finding in Wistar rats. A review of unexposed control groups of many other studies shows that spontaneous lung tumours are very rare in this rat strain (Pott *et al.*, 1995; Table 3.3); on average, the incidence is less than one percent. Therefore, the very high tumour incidences described in this first inhalation study of Wagner *et al.* (1974) might be a misinterpretation of histopathological lesions because of a lack of experience at that time.

In a study conducted by Davis *et al.* (1978), five groups of Wistar rats were exposed to chrysotile (2.0, 10 mg/m^3), crocidolite (5.0, 10 mg/m^3), or amosite (10 mg/m^3). The highest tumour incidences (21–38%) were found in the chrysotile-exposed animals. This may be due to the relatively high fraction of fibres longer than 20 µm in the chrysotile dust used in this experiment. In addition to the lung tumours, extrapulmonary neoplasms included a relatively large number of peritoneal connective tissue tumours.

In a further study by Davis *et al.* (1986b), inhalation of short-fibred amosite did not produce tumours in Wistar rats (0/42). In contrast, there was a tumour incidence of 13/40 (33%) in a group exposed to long-fibred amosite. [The Working Group noted that extensive milling to produce short fibres may have altered the surface reactivity, see Section 4].

A group of 48 SPF Fischer rats was exposed to 10 mg/m^3 UICC chrysotile B by inhalation for 7 hours per day, 5 days per week, for 12 months (Wagner *et al.*, 1984b). This group served as positive controls in a study in which various man-made fibres were tested. After exposure, the animals were kept until natural death. Twelve thoracic tumours (one adenoma, 11 adenocarcinomas) were observed in 48 rats. In the untreated control group, no lung tumours were observed in 48 rats.

Smith *et al.* (1987) exposed groups of 58 female Osborne-Mendel rats to 7 mg/m^3 UICC crocidolite asbestos for 6 hours per day, for 5 days per week, for 2 years. After this treatment, rats were observed for life. The tumour incidence in rats exposed to crocidolite was 3/57 (one mesothelioma and two carcinomas). In the control group, no tumours were observed in 184 rats.

Special attention should be drawn to the crocidolite study with male Fischer rats of McConnell *et al.* (1994) because this study is very well documented. The exposure to 10 mg dust/m^3 (with 1610 WHO fibres/mL containing 236 fibres > 20 µm) for 6 h per day, 5 days per week had to be stopped after 10 months because of unexpected mortality, which was interpreted as a sign that the maximum tolerated dose had been exceeded. The number of WHO fibres per µg dry

Table 3.1 Studies of cancer in experimental animals exposed to various asbestos species and erionite (inhalation exposure)[a]

Test substance	Concentration (mg/m^3)	Aerosol fibres per mL (L > 5 µm)	Species and strain, observation time	Duration of exposure	Number of pleural mesothelioma	No. of animals with thoracic tumours[b]/ No. of animals examined	% tumours	Comments	Reference
Asbestos									
Chrysotile, Canada	86	NR	White rats 16 months or longer	6 h/d 5 d/wk 62 wk	0	10/41[c]	24		Gross *et al.* (1967)
Crocidolite	50	1105	Sprague-Dawley rats lifetime	4 h/d 4 d/w 24 mo	0	5/46	11		Reeves *et al.* (1974)
Chrysotile UICC/A	14.7	NR	Wistar rats lifetime	7 h/d 1 d	0	5/45	11		Wagner *et al.* (1974)
	12.3	NR	Wistar rats lifetime	7 h/d 5 d/wk 3 mo	0	16/36	44		
	10.7	NR	Wistar rats lifetime	7 h/d 5 d/wk 6 mo	0	8/19	42		
	10.9	NR	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	0	19/27	70		
	10.1	NR	Wistar rats lifetime	7 h/d 5 d/wk 24 mo	0	11/17	65		

Table 3.1 (continued)

Test substance	Concentration (mg/m^3)	Aerosol fibres per mL (L > 5 µm)	Species and strain, observation time	Duration of exposure	Number of pleural mesothelioma	No. of animals with thoracic tumours[b]/ No. of animals examined	% tumours	Comments	Reference
Chrysotile UICC/B	9.7	NR	Wistar rats lifetime	7 h/d 1 d	0	1/42	2		
	12.1	NR	Wistar rats lifetime	7 h/d 5 d/wk 3 mo	0	18/34	53		
	10.2	NR	Wistar rats lifetime	7 h/d 5 d/wk 6 mo	0	5/17	29		
	10.7	NR	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	3	14/23	61		
	10.1	NR	Wistar rats lifetime	7 h/d 5 d/wk 24 mo	1	11/21	52		
Crocidolite UICC	12.5	NR	Wistar rats lifetime	7 h/d 1 d	1	7/43	16		
	12.6	NR	Wistar rats lifetime	7 h/d 5 d/wk 3 mo	1	15/36	42		
	10.7	NR	Wistar rats lifetime	7 h/d 5 d/wk 6 mo	0	4/18	22		
	10.6	NR	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	2	20/26	77		
	10.3	NR	Wistar rats lifetime	7 h/d 5 d/wk 24 mo	0	13/18	72		

Table 3.1 (continued)

Test substance	Concentration (mg/m^3)	Aerosol fibres per mL (L > 5 μm)	Species and strain, observation time	Duration of exposure	Number of pleural mesothelioma	No. of animals with thoracic tumours[b]/ No. of animals examined	% tumours	Comments	Reference
Amosite UICC	14.1	NR	Wistar rats lifetime	7 h/d 1 d	1	4/45	9		
	12.4	NR	Wistar rats lifetime	7 h/d 5 d/wk 3 mo	0	10/37	27		
	11.2	NR	Wistar rats lifetime	7 h/d 5 d/wk 6 mo	0	2/18	11		
	10.8	NR	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	0	10/25	40		
	10.6	NR	Wistar rats lifetime	7 h/d 5 d/wk 24 mo	0	13/21	62		
Anthophyllite UICC	12.8	NR	Wistar rats lifetime	7 h/d 1 d	0	2/44	5		
	13.5	NR	Wistar rats lifetime	7 h/d 5 d/wk 3 mo	0	6/37	16		
	10.9	NR	Wistar rats lifetime	7 h/d 5 d/wk 6 mo	0	6/18	33		
	11.4	NR	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	1	21/28	75		
	10.6	NR	Wistar rats lifetime	7 h/d 5 d/wk 24 mo	1	17/18	94		
Amosite UICC	10	550	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	0	2/43	5		Davis *et al.* (1978)

Table 3.1 (continued)

Test substance	Concentration (mg/m^3)	Aerosol fibres per mL (L > 5 µm)	Species and strain, observation time	Duration of exposure	Number of pleural mesothelioma	No. of animals with thoracic tumours[b]/ No. of animals examined	% tumours	Comments	Reference
Crocidolite UICC	5	430	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	1	3/43	7		
	10	860	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	0	1/40	3		
Chrysotile SFA	10.8	430	Wistar rats lifetime	7.5 h/d 5 d/wk 3 mo	1	1/40	3		Wagner *et al.* (1980)
	10.8	430	Wistar rats lifetime	7.5 h/d 5 d/wk 6 mo	0	4/18	22		
	10.8	430	Wistar rats lifetime	7.5 h/d 5 d/wk 12 mo	0	8/22	36		
Chrysotile grade 7	10.8	1020	Wistar rats lifetime	7.5 h/d 5 d/wk 3 mo	0	1/39	3		
	10.8	1020	Wistar rats lifetime	7.5 h/d 5 d/wk 6 mo	0	5/18	28		
	10.8	1020	Wistar rats lifetime	7.5 h/d 5 d/wk 12 mo	0	3/24	13		
Chrysotile UICC (/B)	10.8	3750	Wistar rats lifetime	7.5 h/d 5 d/wk 3 mo	0	4/40	10		
	10.8	3750	Wistar rats lifetime	7.5 h/d 5 d/wk 6 mo	0	10/18	56		
	10.8	3750	Wistar rats lifetime	7.5 h/d 5 d/wk 12 mo	0	6/23	26		

Table 3.1 (continued)

Test substance	Concentration (mg/m^3)	Aerosol fibres per mL (L > 5 μm)	Species and strain, observation time	Duration of exposure	Number of pleural mesothelioma	No. of animals with thoracic tumours[b]/ No. of animals examined	% tumours	Comments	Reference
Chrysotile UICC /A	2	390	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	1	9/42	21		Davis *et al.* (1978)
Chrysotile UICC /A	10	1950	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	0	15/40	38		
Chrysotile UICC	9	NR	Wistar rats lifetime	7 h/d 1 d/wk 12 mo	0	6/43	14	Peak dosing (one d/wk); no control group	Davis *et al.* (1980a)
Amosite UICC	50	NR	Wistar rats lifetime	7 h/d 1 d/w 12 mo	0	6/44	14	Peak dosing (one d/wk); no control group	
Chrysotile UICC	10	NR	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	0	15/43 (8 malignant, 7 benign)	35	No control group	Davis *et al.* (1980b)
Chrysotile "factory"	10	NR	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	0	11/42 (3 maligant, 8 benign)	26	No control group	
Amosite "factory"	10	NR	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	0	0/37	0	No control group	
Amosite UICC	10	NR	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	0	2/40	5	No control group	
Tremolite	10	1600	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	2	20/39	51		Davis *et al.* (1985)
Crocidolite UICC	10	1630/350[d]	Fischer rats lifetime	7 h/d 5 d/wk 12 mo	0	1/28	4		Wagner *et al.* (1985)
Chrysotile WDC textile yarn	3.5	679	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	0	18/41	44		Davis *et al.* (1986a)

Table 3.1 (continued)

Test substance	Concentration (mg/m^3)	Aerosol fibres per mL (L > 5 µm)	Species and strain, observation time	Duration of exposure	Number of pleural mesothelioma	No. of animals with thoracic tumours[b]/ No. of animals examined	% tumours	Comments	Reference
Chrysotile factory WDC	3.7	468	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	0	21/44	48		
Chrysotile textile yarn	3.5	428	Wistar rats lifetime	7 h/d 5 /wk 12 mo	1	16/42	38		
Chrysotile experimental WDC	3.5	108	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	4	21/43	49		
Chrysotile experimental WDC reversed daylight	3.8	111	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	1	18/37	49		
Amosite "long"	10	2060/1110[d]	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	2	13/40	33		Davis *et al.* (1986b)
Amosite "short"	10	70/12[d]	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	0	0/42	0		
Crocidolite UICC	10	NR	Fischer rats lifetime	6 h/d 5 d/wk 12 mo	0	1/28	4		Wagner *et al.* (1987)
Chrysotile, Canada, "long"	10	5510/1930[d]	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	2	22/40	55	1 peritoneal mesothelioma was observed in addition	Davis & Jones (1988)
Chrysotile, Canada, "short"	10	1170/330[d]	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	0	7/40	18	1 peritoneal mesothelioma was observed in addition	
Chrysotile UICC/A "discharged"	10	2670	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	1	11/39	28		Davis *et al.* (1988)

Table 3.1 (continued)

Test substance	Concentration (mg/m^3)	Aerosol fibres per mL (L > 5 µm)	Species and strain, observation time	Duration of exposure	Number of pleural mesothelioma	No. of animals with thoracic tumours[b]/ No. of animals examined	% tumours	Comments	Reference
Chrysotile UICC/A	10	2560	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	0	14/36	39		
Chrysotile UICC /A	10	2560	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	0	13/37	35		Davis *et al.* (1991a)
Chrysotile UICC /A	10	2545	Wistar rats lifetime	5 h/d 5 d/w 12 mo	2	26/41	63	Increase of tumour rate by particulate dust	
+ titanium dioxide	+ 10	-		+ 2 h/d 5 d/w 12 mo					
Chrysotile UICC /A	10	1960	Wistar rats lifetime	5 h/d 5 d/w 12 mo	6	22/38	58	Increase of tumour rate by particulate dust	
+ quartz S600	+ 2	-		+ 2 h/d 5 d/w 12 mo					
Amosite "long"	10	3648	Wistar rats lifetime	5 h/d 5 d/w 12 mo	2	20/40	50	Increase of tumour rate by particulate dust	Davis *et al.* (1991a)
+ titanium dioxide	+ 10	-		+ 2 h/d 5 d/w 12 mo					
Amosite "long"	10	4150	Wistar rats lifetime	5 h/d 5 d/w 12 mo	8	26/39	67	Increase of tumour rate by particulate dust	
+ quartz S600	+ 2	-		+ 2 h/d 5 d/w 12 mo					
Chrysotile Jeffrey	11	NR	Fischer rats lifetime	6 h/d 5 d/wk 12 mo	0	20/52	38		Mc Connell *et al.* (1991)

Table 3.1 (continued)

Test substance	Concentration (mg/m^3)	Aerosol fibres per mL (L > 5 µm)	Species and strain, observation time	Duration of exposure	Number of pleural mesothelioma	No. of animals with thoracic tumours[b]/ No. of animals examined	% tumours	Comments	Reference
Chrysotile	NR	NR	Baboons 6 yr	6 h/d 5 d/wk 4 years	0	0/6[e]	0		Goldstein & Coetzee (1990)
Crocidolite UICC	12-14	1130-1400	Baboons 6 yr	6 h/d 5 d/wk 4 yr	3	3/21[f]	14		
Amosite UICC	7	1110	Baboons 6 yr	6 h/d 5 d/wk 4 yr	2	2/11[f]	18		Goldstein & Coetzee (1990), Webster *et al.* (1993)
Erionite									
Erionite, Oregon	10	354	Fischer rats lifetime	7 h/d 5 d/wk 12 mo	27	27/28	96		Wagner *et al.* (1985)
Erionite, Oregon	NR	NR	Fischer rats lifetime	7 h/d 5 d/wk 12 mo	24	24/27	89	No control group	Wagner (1990)
Erionite, Oregon "short"	NR	NR	Fischer rats lifetime	7 h/d 5 d/wk 12 mo	0	0/24	0	No control group	

[a] negative control groups: see Table 3.3

[b] Animals with benign or malignant lung tumour or pleural mesothelioma. The percentage of animals with tumours is related to the number of rats examined which were alive at a certain point in time (e.g. at the beginning of the experiment or after one year, or at the point in time of the death of the first animal with a tumour). Often, this is not clearly specified.

[c] observation time ≥6 mo

[d] Fibre count refers to fibres with lengths > 10 µm and diameters < 1 µm, in the aerosol

[e] observation time ≥4 yr

[f] observation time ≥5 yr

d, day or days; h, hour or hours; mo, month or months; NR, not reported; wk, week or weeks; yr, year or years

From Pott & Roller (1993b)

Table 3.2 Studies of cancer in experimental animals in which asbestos was used as positive control group (in inhalation studies of various man-made mineral fibres)

Test substance	Concentration (mg/m^3)	Aerosol fibres per cm^3 (L > 5 µm)	Species and strain (No. at risk); Observation time	Duration of exposure	Number of pleural mesothelioma	No. of animals with thoracic tumours[a] / No. of animals	% tumours	Comments	Reference
Amosite	NR	981 89 f > 20 µm/ cm^3	AF/HAN rats, 24 mo	7 h/d 5 d/wk 12 mo	2	18/42 (7 carcinomas, 9 adenomas)	43		Davis *et al.* (1996), Cullen *et al.* (2000)
Chrysotile UICC/B	10	NR	Fischer rats, lifetime	7 h/d 5 d/wk 12 mo	0	11/56 (7 adenocarcinomas, 4 adenomas)	20		McConnell *et al.* (1984)
Chrysotile UICC/B	10	3832/1513[b]	Fischer rats, lifetime	7 h/d 5 d/wk 12 mo	0	12/48 (11 adenocarcinomas, 1 adenoma)	25		Wagner *et al.* (1984b)
Chrysotile NIEHS, Canada	10	10 600	Fischer rats, 24 mo	6 h/d 5 d/wk 24 mo	1	14/69	20		Hesterberg *et al.* (1993)
Crocidolite	10	1610	Fischer 344/N rats, 24 mo	6 h/d 5 d/wk 10 mo	1	14/106 (10 adenomas, 5 carcinomas)	13		McConnell *et al.* (1994)
Crocidolite UICC	7	3000/90[b]	Osborne-Mendel rats, lifetime	6 h/d 5 d/wk 24 mo	1	3/57 (1 mesothelioma, 2 carcinomas)	5		Smith *et al.* (1987)
Chrysotile UICC/A	Cumulative dose: 13 800 mg.h/ m^3	NR	Rats, lifetime	6 h/d 5 d/wk 18 mo	0	9/39 (5 adenomas, 1 adenocarcinoma, 3 squamous cell carcinomas)	23	Strain not specified	Pigott & Ishmael (1982)
Amosite UICC	300	3090	Sprague-Dawley rats, 18–24 mo	6 h/d 5 d/wk 3 mo	0	3/16[c]	19	Small number of animals; D= 0.4 µm	Lee *et al.* (1981), Lee & Reinhardt (1984)
Chrysotile, Canada	5	5901	Wistar rats, 24 mo	5 h/d 5 d/wk 12–24 mo	0	9/47	19		Le Bouffant *et al.* (1987)
Chrysotile Calidria	6	131	Wistar rats, 24 mo	5 h/d 4 d/wk 12 mo	0	0/50	0		Muhle *et al.* (1987)

Table 3.2 (continued)

Test substance	Concentration (mg/m³)	Aerosol fibres per cm³ (L > 5 µm)	Species and strain (No. at risk); Observation time	Duration of exposure	Number of pleural mesothelioma	No. of animals with thoracic tumours[a] / No. of animals	% tumours	Comments	Reference
Crocidolite, South Africa	2.2	162	Wistar rats, 24 mo	5 h/d 4 d/wk 12 mo	0	1/50	2		Muhle *et al.* (1987)
Amosite UICC	300	3090	Syrian golden hamsters, 18–24 mo	6 h/d 5 d/wk 3 mo	0	0/12	0	Small number of animals diameter, 0.4 µm	Lee *et al.* (1981), Lee & Reinhardt (1984)
Crocidolite UICC	7	3000/90[b]	Syrian golden hamsters, lifetime	6 h/d 5 d/wk 24 mo	0	0/58	0		Smith *et al.* (1987)
Amosite	0.8	36 WHO f/cm³ 10 f> 20 µm/cm³	Syrian golden hamsters, 84 wk	6 h/d 5 d/wk 78 wk	3	3/83	3.6		McConnell *et al.* (1999)
	3.7	165 WHO f/cm³ 38 f> 20 µm/cm³	Syrian golden hamsters, 84 wk	6 h/d 5 d/wk 78 wk	22	22/85	26		
	7.1	263 WHO f/cm³ 69 f> 20 µm/cm³	Syrian golden hamsters, 84 wk	6 h/d 5 d/wk 78 wk	17	17/87	20		
Crocidolite UICC	13.5	1128	Baboons lifetime	7 h/d 5 d/wk 40 mo	0	0/10	0	All males	Goldstein *et al.* (1983)

[a] *n* = animals with benign or malignant lung tumour or pleural mesothelioma

[b] Number of fibres with a length > 10 µm and a diameter < 1 µm in the aerosol

d, day or days; f, fibre; h, hour or hours; mo, month or months; NR, not reported; RCF, refractory ceramic fibre; wk, week or weeks

From Pott & Roller (1993b)

Table 3.3 Negative controls (clean air for lifetime) in carcinogenicity studies after inhalation exposures from Table 3.1 and Table 3.2

Species and strain	Number of pleural mesothelioma	No. of animals with thoracic tumours[a]/ No. of animals	Reference
Fischer rats	0	0/48	Wagner *et al.* (1984b)
Fischer rats	0	0/28	Wagner *et al.* (1985)
Fischer rats	0	0/28	Wagner *et al.* (1987)
Fischer rats	0	1/56	McConnell *et al.* (1991)
Fischer rats	0	4/123	Hesterberg *et al.* (1993)
Fischer rats	0	2/126	McConnell *et al.* (1994)
Osborne-Mendel rats	0	0/184	Smith *et al.* (1987)
Sprague-Dawley rats	0	1/5	Reeves *et al.* (1974)
Sprague-Dawley rats	0	0/19	Lee *et al.* (1981)
White rats	0	0/25	Gross *et al.* (1967)
Wistar rats	0	7/126	Wagner *et al.* (1974)
Wistar rats	0	0/20	Davis *et al.* (1978)
Wistar rats	0	1/71	Wagner *et al.* (1980)
Wistar rats	0	0/36	Davis *et al.* (1985)
Wistar rats	0	2/39	Davis *et al.* (1986a)
Wistar rats	0	0/25	Davis *et al.* (1986a)
Wistar rats	0	0/110	Muhle *et al.* (1987)
Wistar rats	0	2/36	Davis *et al.* (1988)
Wistar rats	0	0/25	Davis *et al.* (1988)
Wistar rats	0	2/47	Davis & Jones (1988)
Wistar rats	0	2/47	Davis *et al.* (1991a)
Syrian golden hamsters	0	1/170	Smith *et al.* (1987)
Syrian golden hamsters	0	0/83	Mc Connell *et al.* (1999)

[a] *n* = animals with benign or malignant lung tumour or pleural mesothelioma

lung tissue was 1850 (73 fibres > 20 µm) at the end of exposure and 759 WHO fibres (41 fibres > 20 µm) 12 months later. Fourteen out of 106 rats (13.2%), which survived the second year or longer, died with lung tumour (five of these rats developed lung carcinomas), and one rat also developed a mesothelioma. In the control group, 2/126 rats developed lung adenomas.

In two lifetime studies, male and female Fischer rats were exposed to either 10 mg/m^3 erionite (Wagner *et al.*, 1985) or an unknown concentration of erionite (Wagner, 1990) for 6 hours per day, 5 days per week, for 12 months. Twenty seven out of 28 rats, and 24/27 rats developed pleural mesotheliomas, respectively. No lung tumours were observed. [The Working Group noted the lack of control group in the study by Wagner (1990).]

McConnell *et al.* (1999) exposed three groups of 125 male Syrian golden hamsters to 0.8, 3.7 and 7.1 mg/m^3 amosite for 6 hours per day, 5 days per week, for 78 weeks. They were then held unexposed for 6 weeks. Among animals that survived for at least 32 weeks, 3/83, 22/85 and 17/87 developed pleural mesotheliomas, respectively. No mesotheliomas were observed in 83 untreated controls and no lung tumours were observed in any groups.

Some experiments were reported with baboons. After amosite exposure and crocidolite exposure for 4 years, 2/11 baboons and 3/21 baboons developed pleural mesothelioma,

respectively (Goldstein & Coetzee, 1990; Webster *et al.*, 1993).

3.3 Intrapleural and intraperitoneal administration

Animal experiments had shown that an intrapleural injection of a suspension of asbestos dusts in rats leads to mesotheliomas (Wagner, 1962; Wagner & Berry, 1969). The serosa has subsequently been taken as a model for the examination of the carcinogenicity of fibrous dusts in numerous studies. Some groups have opted for administration into the pleural cavity, others preferring intraperitoneal injection of dust suspensions. In comparison with the intrapleural model, the intraperitoneal carcinogenicity test on fibres has proven to be the method with the far greater capacity and, consequently, the greater sensitivity (see also Pott & Roller, 1993a). Results from these numerous experiments using asbestos and erionite are listed in Table 3.4.

Table 3.5 contains a summary of the experiments by Stanton *et al.* (1981). In this extensive study, the authors implanted 72 dusts containing fibres of various sizes in the pleura of Osborne-Mendel rats. The probability of the development of pleural mesotheliomas was highest for fibres with a diameter of less than 0.25 µm and lengths greater than 8 µm.

In summary, samples of all six asbestos types and of erionite were administered to rats by intrapleural or intraperitoneal injection in numerous studies. Consistently, mesothelima induction was observed when samples contained a sufficient fibre number with a fibre length > 5 µm.

3.4 Intratracheal administration

Only a few studies have been carried out with intratracheal instillation of asbestos fibres in rats (Pott *et al.*, 1987; Smith *et al.*, 1987), and hamsters (Pott *et al.*, 1984; Feron *et al.*, 1985; Smith *et al.*, 1987). Principally, in this experimental model, asbestos fibres induced lung tumours in rats, and lung tumours and mesotheliomas in hamsters. Studies in hamsters are described below.

In a 2-year study, a group of male Syrian golden hamsters [initial number unspecified] was intratracheally instilled with 1 mg UICC crocidolite in 0.15 mL saline once a week for 8 weeks. At the end of the experiment, the incidences of lung carcinomas and of pleural mesotheliomas were 9/142 [$P < 0.01$] and 8/142 [$P < 0.01$], respectively. No thoracic tumours were observed in 135 titanium-dioxide-treated control animals (Pott *et al.*, 1984).

In a lifetime study, a group of Syrian golden hamsters [sex and initial number unspecified] was intratracheally instilled with 2 mg UICC crocidolite in 0.2 mL saline once a week for 5 weeks. At the end of the experiment, 20/27 animals developed broncho-alveolar tumours ($p<0.05$), including 7/27 with malignant tumours [$p<0.05$]. No broncho-alveolar tumours were observed in 24 saline-treated controls (Smith *et al.*, 1987).

3.5 Oral administration

A study on the carcinogenicity of ingested asbestos fibres involved male F344 rats groups exposed to amosite or chrysotile in combination with subcutaneous administration of a known intestinal carcinogen, azoxymethane (10 weekly injections of 7.4 mg/kg body weight). Fibres were administered three times a week for 10 weeks by intragastric bolus dosing (10 mg in 1 mL saline). The first experiment in this study included a full set of appropriate control groups. The experiment was terminated at 34 weeks. Neither amosite nor UICC chrysotile B, in combination with azoxymethane, increased the incidence of any intestinal tumours (≈10%) above that produced by azoxymethane alone, but the combination with either fibre type produced 4–5-fold increases

(not significant, $P > 0.1$) in metastatic intestinal tumours. A second experiment with larger groups, the same dosing regimen, and for lifetime, but with a more limited design, tested only amosite in combination with azoxymethane versus azoxymethane. Amosite did not enhance azoxymethane-induced intestinal tumours (incidence, 77% versus 67%) (Ward *et al.*, 1980; IOM, 2006). [The Working Group noted that the lack of untreated vehicle controls in the second experiment made interpretation of the results difficult considering that, compared to historical controls, there was a non-significant increase in intestinal tumours in rats exposed only to amosite (≈33%). One cannot know whether the results observed were associated with the asbestos or with irritation from the procedure, although one would not anticipate that gavage itself would impact the lower portion of the gastrointestinal tract.]

The most definitive animal studies of oral exposure to asbestos were a series of lifetime studies conducted by the National Toxicology Program (NTP, 1983, 1985, 1988, 1990a, b), in which asbestos (chrysotile, crocidolite, and amosite) was administered in the feed of rats and hamsters. Nonfibrous tremolite was also tested in rats according to the same protocol (NTP, 1990c). Exposure of dams of the study animals (1% in the diet) was followed by exposure of the pups by gavage (0.47 mg/g water) while they were nursing, and then in the diet for the remainder of their lives: they were exposed to asbestos at the level of 1%, which was estimated by the investigators to be about 70000 times the greatest possible human exposure in drinking-water. Histopathological examination of the entire colorectum was performed. No increases in the incidence of gastrointestinal lesions (inflammatory, preneoplastic, or neoplastic) were found after exposure to intermediate-length chrysotile (from Quebec) in hamsters, to short chrysotile (from New Idria) in rats or hamsters, to amosite in rats or hamsters, to crocidolite in rats, or to non-fibrous tremolite in rats. The mesentery was examined in detail, as well as mesenteric lymph nodes and sections of the larynx, trachea, and lungs from every animal. No lesions were found in any of those tissues. The only finding of note in the gastrointestinal tract was a slight increase in the incidence of adenomatous polyps in the large intestine after exposure to the intermediate-length chrysotile (from Quebec) in male rats (9/250 versus 0/85, $P = 0.08$), but preneoplastic changes in the epithelium were not found (NTP, 1985; IOM, 2006).

3.6 Intragastric administration

White rats, 2–3 months old, were surgically applied, on the greater curvature of the stomach, a perforated capsule containing 0 (control) or 100 mg chrysotile asbestos in a filler (beef fat: natural wax, 1:1). Tumours observed in 18/75 asbestos-exposed rats, between 18–30 months after the beginning of the experiment, were the following: eight gastric adenomas, two gastric adenocarcinomas, one gastric carcinoma, one cancer of the forestomach, one small intestine adenocarcinoma, two peritoneal mesotheliomas, and three abdominal lymphoreticular sarcomas. No tumours were observed in 75 control animals (Kogan *et al.*, 1987). [The Working Group noted various unresolved questions regarding the design of this study in particular the very high dose of 100 mg.]

3.7 Studies in companion animals

Mesotheliomas were reported in pet dogs with asbestos exposure in the households of their owners. Eighteen dogs diagnosed with mesothelioma and 32 age-, breed- and gender-matched control dogs were investigated. Sixteen owners of cases and all owners of controls were interviewed. An asbestos-related occupation or hobby of a household member was significantly associated with mesothelioma observed in cases (OR,

Table 3.4 Studies of cancer in rats exposed to asbestos fibres and erionite (intrapleural and intraperitoneal administration)

Rat strain Reference	Fibrous dust (material)	Injected mass (mg)	Injection type	No. of fibres [a] [10^9]	Tumour incidence [b]		Significance [c]	Comments
					n/z	%		
Asbestos	**Asbestos type**							
Wistar – Pott *et al.* (1989)	Actinolite	0.25	i.p.	0.1	20/36	56	***	
Wistar – Wagner *et al.* (1973)	Amosite UICC	20	i.pl.	NR	11/32	34	***	
Wistar – Davis *et al.* (1991b)	Amosite from UICC	0.01	i.p.	0.0003	4/48	8	*	
Wistar – Davis *et al.* (1991b)	Amosite from UICC	0.05	i.p.	0.002	8/32	25	***	
Wistar – Davis *et al.* (1991b)	Amosite from UICC	0.5	i.p.	0.02	15/32	47	***	
Wistar – Wagner *et al.* (1973)	Anthophyllite UICC	20	i.pl.	NR	8/32	25	***	
Wistar – Wagner *et al.* (1973)	Chrysotile UICC/A	20	i.pl.	NR	7/31	23	***	
Sprague-Dawley – Monchaux *et al.* (1981)	Chrysotile UICC/A	20	i.pl.	NR	14/33	42	***	
Sprague-Dawley – Wagner *et al.* (1984b)	Chrysotile UICC/A	20	i.pl.	19.6	6/48	13	**	
Wistar – Pigott & Ishmael (1992)	Chrysotile UICC/A	20	i.pl.	NR	7/48	15	***	
Fischer – Coffin *et al.* (1992)	Chrysotile UICC/A	0.5	i.pl.	0.90	118/142[d]	78	***[d]	
		2		3.6		87		
		4		7.2		92		
		8		14		83		
		16		29		83		
		32		57		75		
Wistar – Wagner *et al.* (1973)	Chrysotile UICC/B	20	i.pl.	NR	10/32	31	***	
Wistar – Wagner *et al.* (1980)	Chrysotile UICC/B	20	i.pl.	NR	5/48	10	*	
Fischer – Wagner *et al.* (1987)	Chrysotile UICC/B	20	i.pl.	NR	19/39	49	***	
Wistar – Pott *et al.* (1989)	Chrysotile UICC/B	0.25	i.p.	0.2	23/34	68	***	

Table 3.4 (continued)

Rat strain Reference	Fibrous dust (material)	Injected mass (mg)	Injection type	No. of fibres [a] [10^9]	Tumour incidence [b]		Significance [c]	Comments
					n/z	%		
Wistar – Davis *et al.* (1991b)	Chrysotile from UICC/A	0.01	i.p.	0.002	2/48	4	NS	
Wistar – Davis *et al.* (1991b)	Chrysotile from UICC/A	0.05	i.p.	0.009	12/32	38	***	
Wistar – Davis *et al.* (1991b)	Chrysotile from UICC/A	0.5	i.p.	0.09	26/32	81	***	
Wistar – Wagner *et al.* (1973)	Crocidolite UICC	20	i.pl.	NR	19/32	59	***	
Fischer – Wagner *et al.* (1987)	Crocidolite UICC	20	i.pl.	NR	34/40	85	***	
Fischer – Wagner (1990)	Crocidolite UICC	20	i.pl.	NR	24/32	75	***	
Sprague-Dawley – Monchaux *et al.* (1981)	Crocidolite UICC	20	i.pl.	NR	21/39	54	***	
Osborne-Mendel – Stanton *et al.* (1981)	Crocidolite UICC	40	i.pl.	NR	14/29	48	***	
Fischer – Wagner *et al.* (1984a)	Crocidolite UICC	20	i.pl.	NR	35/41	85	***	
Fischer – Wagner *et al.* (1984a)	Crocidolite UICC ground 1 h	20	i.pl.	NR	34/42	81	***	
Fischer – Wagner *et al.* (1984a)	Crocidolite UICC ground 2 h	20	i.pl.	NR	34/42	81	***	
Fischer – Wagner *et al.* (1984a)	Crocidolite UICC ground 4 h	20	i.pl.	NR	15/41	37	***	
Fischer – Wagner *et al.* (1984a)	Crocidolite UICC ground 8 h	20	i.pl.	NR	13/42	31	***	
Fischer – Coffin *et al.* (1992)	Crocidolite UICC	0.5	i.pl.	0.04	65/144[d]	29	** [d]	
		2		0.16		13		
		4		0.32		50		
		8		0.65		67		
		16		1.3		58		
		32		2.6		54		
Wistar – Davis *et al.* (1991b)	Crocidolite from UICC	0.01	i.p.	0.0004	0/48	0	NS	
Wistar – Davis *et al.* (1991b)	Crocidolite from UICC	0.05	i.p.	0.002	8/32	25	***	

Table 3.4 (continued)

Rat strain Reference	Fibrous dust (material)	Injected mass (mg)	Injection type	No. of fibres [a] [10^9]	Tumour incidence [b]		Significance [c]	Comments
					n/z	%		
Wistar – Davis *et al.* (1991b)	Crocidolite from UICC	0.5	i.p.	0.02	10/32	31	***	
Wistar – Pott *et al.* (1987)	Crocidolite South Africa	0.5	i.p.	0.05	18/32	56	***	
Wistar – Roller *et al.* (1996)	Crocidolite A	0.5	i.p.	0.042	25/32	78	***	All females
Wistar – Roller *et al.* (1996)	Crocidolite A	0.5	i.p.	0.042	32/48	67	***	All females
Wistar – Roller *et al.* (1996)	Crocidolite C	0.5	i.p.	0.042	20/39	51	***	
Wistar – Davis *et al.* (1985)	Tremolite, Korea	25	i.p.	NR	27/29	93	***	
Wistar – Roller *et al.* (1996)	Tremolite B	3.3	i.p.	0.057	9/40	23	***	
Wistar – Roller *et al.* (1996)	Tremolite B	15	i.p.	0.26	30/40	75	***	
Erionite	Erionite type							
Sprague-Dawley – Pott *et al.* (1987)	Karain	1.25	i.p.	NR	38/53	72	***	
Sprague-Dawley – Pott *et al.* (1987)	Karain	5	i.p.	NR	43/53	81	***	
Sprague-Dawley – Pott *et al.* (1987)	Karain	20	i.p.	G	37/53	70	***	
Fischer – Wagner *et al.* (1985)	Karain	20	i.pl.	NR	38/40	95	***	
Fischer – Wagner *et al.* (1985)	Oregon	20	i.pl.	NR	40/40	100	***	
Wistar – Pott *et al.* (1987)	Oregon	0.5	i.p.	0.02	15/31	48	***	
Wistar – Pott *et al.* (1987)	Oregon	2	i.p.	0.08	28/31	90	***	
Fischer – Wagner (1990)	Oregon	20	i.pl.	NR	30/32	94	***	
Fischer – Wagner (1990)	Oregon “short”	20	i.pl.	NR	0/32	0	NS	
Wistar – Davis *et al.* (1991b)	Oregon	0.005	i.p.	0.00025	0/48	0	NS	
		0.01		0.0005	4/48	8	*	
		0.05		0.0025	15/32	47	***	
		0.5		0.025	26/32	81	***	
		2.5		0.125	30/32	94	***	
		5		0.25	21/24	88	***	
		10		0.5	20/24	83	***	
		25		1.25	17/18	94	***	

Table 3.4 (continued)

Rat strain Reference	Fibrous dust (material)	Injected mass (mg)	Injection type	No. of fibres [a] [10^9]	Tumour incidence [b]		Significance [c]	Comments
					n/z	%		
Porton – Hill *et al.* (1990)	Oregon	0.1	i.pl.	NR	5/10	50	*	
		1		NR	9/10	90	***	
		10		NR	9/10	90	***	
		20		NR	8/10	80	***	
Wistar – Kleymenova *et al.* (1999)	Grusia mines	20	i.pl.	NR	39/40	98	?	
Fischer – Coffin *et al.* (1992)	Oregon "C"	0.5	i.pl.	NR	123/144[d]	79	***[d]	
		2		NR		87		
		4		NR		83		
		8		NR		84		
		16		NR		87		
		32		NR		91		
Fischer – Coffin *et al.* (1992)	Oregon "W"	0.5	i.pl.	NR	137/144[d]	100	***[d]	
		2		NR		92		
		4		NR		100		
		8		NR		91		
		16		NR		96		
		32		NR		92		
Sprague-Dawley – Maltoni & Minardi (1989)	"Sedimentary erionite"	25	i.pl.	NR	35/40	88	***	
Sprague-Dawley – Maltoni & Minardi (1989)	"Sedimentary erionite"	25	i.p.	NR	35/40	50	***	

[a] The fibre numbers mainly refer to fibres with a length greater than 5 µm
[b] n/z number of animals with serosal tumour (mesothelioma/sarcoma) / number of animals examined
[c] calculation of the statistical significance with the Fisher exact test, one-sided: *** $p < 0.001$; ** $p < 0.01$; * $p \leq 0.05$
[d] combined data of 6 groups
i.p., intrapleural; i.pl., intraperitoneal; NS, not significant; NR, not reported
From Pott & Roller (1993b)

Table 3.5 Carcinogenicity study of intrapleural application of asbestos fibres and other fibrous materials in female Osborne-Mendel rats (40 mg fibres per rat)

Fibrous dust (material)	No. of fibres [a] (x10^6) L > 8 µm D < 0.25 µm	Probability of pleural sarcomas [b]		Pleural sarcoma incidence [c]	
				n/z	%
Tremolite 1	55	100		22/28	79
Tremolite 2	28	100		21/28	75
Crocidolite 1	6500	94	± 6.0	18/27	67
Crocidolite 2	800	93	± 6.5	17/24	71
Crocidolite 3	4100	93	± 6.9	15/23	65
Amosite	140	93	± 7.1	14/25	56
Crocidolite 4	5400	86	± 9.0	15/24	63
Crocidolite 5 (UICC)	78	78	± 10.8	14/29	48
Crocidolite 6	1600	63	± 13.9	9/27	33
Crocidolite 7	18	56	± 11.7	11/26	42
Crocidolite 8	< 0.3[d]	53	± 12.9	8/25	32
Crocidolite 9	710	33	± 9.8	8/27	30
Crocidolite 10	49	37	± 13.5	6/29	21
Crocidolite 11	< 0.3[d]	19	± 8.5	4/29	14
Crocidolite 12	220	10	± 7.0	2/27	7
Talc 1	< 0.3[d]	7	± 6.9	1/26	4
Talc 3	< 0.3[d]	4	± 4.3	1/29	3
Talc 2	< 0.3[d]	4	± 3.8	1/30	3
Talc 4	< 0.3[d]	5	± 4.9	1/29	3
Crocidolite 13	< 0.3[d]	0		0/29	0
Talc 5	< 0.3[d]	0		0/30	0
Talc 6	80	0		0/30	0
Talc 7	< 0.3[d]	0		0/29	0

[a] Fibre numbers stated in original work as common logarithm.

[b] Calculation taking into account the different life spans (life table method).

[c] n/z = number of rats with pleural sarcomas/number of rats examined. Frequency of pleural sarcomas in female control rats: untreated, 3 animals out of 491 (0.6%); with non-carcinogenic lung implantates, 9 out of 441 (2.0%); with non-carcinogenic pleural implantates, 17 out of 615 (2.8%). [17 out of 615 against 3 out of 491, according to Fisher exact test $P < 0.01$]. All three control groups are brought together by Stanton *et al.* (1981) to 29 out of 1518 animals (1.9%); for this after application of the life table method a tumour probability of 7.7 ± 4.2% is indicated. [Without any reason being given it is concluded that the tumour probability in any one of the groups treated according to the life table method must exceed 30% to be "significantly" increased.] Significance limit for Fisher test in the case of 25 to 30 animals against 17 out of 615 control rats: approx. 12 to 13% tumour frequency. (The term "tumour frequency" is not to be equated with tumour probability according to the life table method. The "significance limit" of 30% mentioned by Stanton *et al.* (1981) refers to life table incidence or probability.

[d] The de-logarithmised fibre numbers with the above mentioned definition are between 0 and 0.3.

From Stanton *et al.* (1981)

8.0; 95%CI: 1.4–45.9). Lung tissue from three dogs with mesothelioma and one dog with squamous cell carcinoma of the lung had higher level of chrysotile asbestos fibres than lung tissue from control dogs (Glickman *et al.*, 1983).

3.8 Synthesis

Bronchial carcinomas and pleural mesotheliomas were observed in many experiments in rats after exposure to chrysotile, crocidolite, amosite, anthophyllite, and tremolite fibres. In these studies, there was no consistent increase in tumour incidence at other sites. A special preparation of "long" crocidolite was more effective to induce lung tumours compared to the "short" UICC asbestos samples on the basis of administered dose in f/mL.

In one study in Syrian golden hamsters with three different concentrations of amosite, a significant increase in pleural mesothelioma incidence was observed, but no lung tumours were found.

After amosite exposure and crocidolite exposure by inhalation, 2/11 baboons and 3/21 baboons developed pleural mesothelioma, respectively.

In two studies in rats exposed to erionite, a significant increase in pleural mesothelioma incidence was observed. However, no lung tumours were found.

Samples of all six asbestos types and of erionite were administered to rats by intrapleural or intraperitoneal injection in numerous studies. Consistently, mesothelioma induction was observed when samples contained a sufficient fibre number with a fibre length > 5 µm.

Only a few studies have been carried out with intratracheal instillation of crocidolite in rats and hamsters. Malignant lung tumours were observed in rats, and pleural mesothelioma and malignant lung tumours were observed in hamsters.

Chrysolite, crocidolite and amosite were administered in the feed of rats and hamsters. No increase of the incidence of gastrointestinal tumours was observed in both species.

No chronic studies with vermiculite containing asbestos fibres or talc containing asbestos fibres could be identified.

4. Other Relevant Data

4.1 Toxicokinetics, deposition, clearance, and translocation in humans

4.1.1 Aerodynamic and anatomical factors

Inhalation is the most important route of exposure to mineral fibres, and is associated with the development of non-malignant diseases of the lungs and pleura, and malignant diseases arising in the lung, larynx, and pleural and peritoneal linings (IOM, 2006). The deposition of particles and fibres in the lungs is dependent on their aerodynamic diameter, which is a function of geometry, aspect ratio (IARC, 2002), and density (Bernstein *et al.*, 2005). Fibres can deposit by sedimentation, by impaction at bronchial bifurcations or by interception of the fibre tip with the bronchial wall. Smaller diameter fibres are likely to deposit in the alveoli (Bernstein *et al.*, 2005).

Particles and fibres can be cleared from the nasal and tracheobronchial regions by mucociliary transport (Lippmann *et al.*, 1980). Following deposition in the distal airways and alveoli, short fibres are removed more slowly following phagocytosis by alveolar macrophages. Fibre length is a limiting factor in macrophage-mediated clearance; fibres longer than the diameter of human alveolar macrophages (approximately 14–25 µm) are less likely to be cleared. Fibres may also interact with lung epithelial cells, penetrate into the interstitium, and translocate to the pleura and peritoneum or more distant sites. Fibres that are not efficiently cleared or altered by physicochemical process (e.g. breakage, splitting, or

chemical modification) are termed biopersistent (Bernstein *et al.*, 2005). Chronic inhalation assays using man-made fibres in rodents have correlated fibre length and biopersistence with persistent inflammation, fibrosis, lung cancer, and malignant mesothelioma (Bernstein *et al.*, 2005). However, there are interspecies differences in alveolar deposition of inhaled particles and fibres that must be considered when extrapolating results of rodent inhalation studies to humans (IARC, 2002).

4.1.2 Biopersistence of asbestos and erionite fibres

Asbestos fibres and ferruginous bodies (described subsequently in Section 4.3.1) can be identified and quantified by tissue digestion of lung samples obtained by biopsy or at autopsy (Roggli, 1990). A variety of commercial and non-commercial asbestos fibres have been identified in residents older than 40 years of age living in an urban area with no history of occupational asbestos exposure (Churg & Warnock, 1980). These and other studies confirm that asbestos fibres are biopersistent and accumulate in lung tissue as well as lymph nodes (Dodson *et al.*, 1990; Dodson & Atkinson, 2006). Asbestos fibres have also been identified in the pleura following autopsy (Dodson *et al.*, 1990; Gibbs *et al.*, 1991; Suzuki & Yuen, 2001) and in the parietal pleural in samples collected during thoracoscopy (Boutin *et al.*, 1996). Roggli *et al.* (1980) also identified asbestos bodies in the larynx of asbestos workers at autopsy. Systemic translocation of asbestos fibres to distant organs has also been described in case reports; however, these reports should be evaluated with caution due to the numerous caveats in technical procedures used, comparison with an appropriate control population, and cross-contamination of tissue samples (Roggli, 2006). The route of translocation of asbestos fibres from the lungs to distant sites is unknown, although lymphatic translocation of amosite fibres deposited in the lungs has been shown in experimental animals (Hesterberg *et al.*, 1999; Mc Connell *et al.*, 1999; IOM, 2006; NIOSH, 2009).

Environmental exposure to erionite fibres is associated with diffuse malignant mesothelioma in three rural villages in the Cappadocia region of Turkey (Baris & Grandjean, 2006). Lung fibre digests obtained from humans in these villages showed elevated levels of erionite fibres, and ferruginous bodies surrounding erionite fibres were found in broncho-alveolar lavage fluid (Sébastien *et al.*, 1984; Dumortier *et al.*, 2001).

Talc particles have been found in the lungs at autopsy of both rural and urban residents as well as talc miners (IARC, 1987b, 2010). Talc particles are biopersistent in the lungs, and have been recovered in broncho-alveolar lavage fluid obtained from workers 21 years after cessation of occupational exposure (Dumortier *et al.*, 1989). Talc contaminated with asbestos has been linked to the development of lung cancer and malignant mesothelioma (IARC, 1987b).

The association between exposure to talc, potential retrograde translocation to the ovarian epithelium, and the development of ovarian cancer is controversial (IARC, 2010, and this volume).

The biological plausibility for an association between asbestos and ovarian cancer derives in part from the finding of asbestos fibres in the ovaries of women with potential for exposure to asbestos. Thus, a histopathological study of ovaries from 13 women who had household contact with men who had documented exposure to asbestos, and of 17 women who gave no history of potential for asbestos exposure found "significant asbestos fibre burdens" in the ovaries of nine (60.2%) of the exposed women and in only six (35%) of the unexposed women. Three of the exposed women had asbestos fibre counts in ovarian tissue of over 1 million fibres per gram (wet weight), but only one of the 17

women without exposure had counts in that range (Heller *et al.*, 1996).

Further support for the biological plausibility of an association between asbestos exposure and ovarian cancer derives from an experimental study (Graham & Graham, 1967) that found that the intraperitoneal injection of tremolite asbestos into guinea-pigs and rabbits produced epithelial changes in the ovaries "similar to those seen in patients with early ovarian cancer".

[The Working Group noted that the histopathological diagnosis of ovarian carcinoma is difficult and requires the application of immunohistochemical techniques to distinguish between this cancer and peritoneal malignant mesothelioma. These techniques and the recognition of borderline ovarian tumours and variants of serosal tumours that arise in the pelvis of women were not applied in the Graham & Graham study in 1967. In addition, mesothelial hyperplasia occurs commonly in the pelvic region, and is not considered a preneoplastic lesion (NIOSH, 2009).]

4.2 Molecular pathogenesis of human cancers related to mineral dust exposure

Cancers develop in the upper and lower respiratory tract (carcinoma of the larynx and lungs), and in the pleural and peritoneal linings (diffuse malignant mesothelioma) after a long latent period up to 20–40 years following initial exposure to asbestos or erionite fibres (IARC, 1977; IOM, 2006). During the long latent period before the clinical diagnosis of cancer of the lung or of the larynx or diffuse malignant mesothelioma, multiple genetic and molecular alterations involving the activation of cell growth regulatory pathways, the mutation or amplification of oncogenes, and the inactivation of tumour–suppressor genes characterize specific histopathological types of these tumours that have been associated with exposure to mineral dust or fibres. Some of these molecular alterations have been linked to specific chemical carcinogens in tobacco smoke (Nelson & Kelsey, 2002), and additional alterations may arise secondarily due to chronic inflammation, genetic instability, or epigenetic changes that will be discussed in detail in Section 4.3.

Additional pathways related to resistance to apoptosis, acquired genetic instability, and angiogenesis are activated or upregulated during the later stages of tumour progression of lung cancer and diffuse malignant mesothelioma (Table 4.1; Table 4.2). No mutations in oncogenes or tumour-suppressor genes have been directly linked with exposure to asbestos fibres (NIOSH, 2009).

4.2.1 Cancer of the lung and of the larynx

Lung cancers are classified into two histological subtypes: small cell carcinoma and non-small cell carcinoma (Table 4.1). In non-small cell lung carcinoma, activating point mutations in the *K-RAS* oncogene have been linked to specific chemical carcinogens in tobacco smoke; Nelson *et al.* (1999) described more frequent *K-RAS* mutations in lung carcinomas in asbestos-exposed workers. Loss of heterozygosity and point mutations in the *p53* tumour-suppressor gene have also been linked with tobacco smoke carcinogens in cancer of the lung and of the larynx (Pfeifer *et al.*, 2002; NIOSH, 2009). These alterations have also been described in lung cancers in asbestos-exposed workers (Nymark *et al.*, 2008).

4.2.2 Diffuse malignant mesothelioma

Malignant tumours arising in the pleural or peritoneal linings (diffuse malignant mesothelioma) have no association with tobacco smoking, and are characterized by a different spectrum of molecular alterations (Table 4.2). In contrast with lung cancers associated with tobacco smoking and asbestos exposure, mutations in the *K-RAS*

Table 4.1 Some reported molecular alterations in bronchogenic carcinoma

Functional alterations	Gene target	Histological type of lung cancer	
		Small cell	Non-small cell
Autocrine growth stimulation	Growth factors and receptors	GRP/GRP receptor SCF/KIT	TGF-α/EGFR HGF/MET
Activation of oncogenes	*RAS* mutation	<1%	15–20%
	MYC overexpression	15–30%	5–10%
Inactivation of tumour-suppressor genes	*p53* mutation	~90%	~50%
	RB mutation	~90%	15–30%
	$p16^{INK4A}$ inactivation	0–10%	30–70%
	FHIT inactivation	~75%	50–75%
Resistance to apoptosis	*BCL2* expression	75–95%	10–35%
Genetic instability	Microsatellite instability	~35%	~22%

EGFR, epidermal growth factor receptor; FHIT, fragile histidine triad; GRP, gastrin-releasing peptide; HGF, hepatocyte growth factor; RB, retinoblastoma gene; SCF, stem cell factor; TGF-α, transforming growth factor-α.
From Sekido *et al.* (2001), Sato *et al.* (2007), Schwartz *et al.* (2007), NIOSH (2009)

oncogene or the *p53* tumour-suppressor gene are rare. The most frequent molecular alteration involves deletion or hypermethylation at the *CDKN2A/ARF* locus on chromosome 9p21 which contains three tumour-suppressor genes: *p15*, $p16^{INK4A}$, and $p14^{ARF}$ (Murthy & Testa, 1999). Additional molecular alterations include hypermethylation and silencing of the *RASSFIA* and *GPC3* tumour-suppressor genes, and inactivation of the *NF2* tumour-suppressor gene (Apostolou *et al.*, 2006; Murthy *et al.*, 2000).

Comparative genomic hydrizidation, gene expression profiling, and proteomics have been used to identify specific diagnostic and prognostic biomarkers for diffuse malignant mesothelioma (Wali *et al.*, 2005; Greillier *et al.*, 2008). The most promising outcome of these global screening strategies is the identification of two potential serum or pleural fluid biomarkers that may provide early diagnosis of malignant pleural mesothelioma: osteopontin (Pass *et al.*, 2005), and soluble mesothelin-related protein (Robinson *et al.*, 2005). Both of these markers have been shown to be elevated in most patients diagnosed with diffused malignant mesothelioma, but are not entirely specific for these cancers (Greillier *et al.*, 2008). No gene expression signature can be attributed directly to asbestos exposure, and these studies show variable gene expression patterns resulting from limited stability of RNA, contamination of tumour samples with host cells, and use of different microarray platforms (López-Ríos *et al.*, 2006).

In addition to the genetic and chromosomal alterations that have been identified in diffuse malignant mesothelioma (Table 4.2), epigenetic alterations characterized by altered patterns of DNA methylation have been described (Toyooka *et al.*, 2001; Tsou *et al.*, 2005). Overall, human tumours have been characterized by global hypomethylation associated with hypermethylation of CpG islands in the promoter regions of tumour-suppressor genes leading to their inactivation. These alterations in DNA methylation are the most common molecular or genetic lesion in human cancer (Esteller, 2005). Recent comprehensive analyses of epigenetic profiles of 158 patients with malignant pleural mesotheliomas and 18 normal pleural samples using 803 cancer-related genes revealed classes of methylation profiles in malignant mesothelioma that were associated with asbestos lung burden and survival (Christensen *et al.*, 2009). Other data confirmed hypermethylation of cell-cycle

Table 4.2 Some reported molecular alterations in diffuse malignant mesothelioma

Function	Gene target	Alteration
Autocrine growth stimulation	Growth factors and receptors	HGF/MET upregulation EGFR upregulation PDGF upregulation IGF-1 upregulation
Tumour-suppressor genes	*p15, p16^{INK4A}, p14^{ARF}*	Inactivation or deletion
	Neurofibromin 2	*NF2* deletions, mutations
	RASSF1A, GPC3	Hypermethylation
Angiogenesis	VEGF	Upregulation
Apoptosis	*AKT*	Constitutive activation
	BCL-X	Upregulation

EGFR, epidermal growth factor receptor; HGF, hepatocyte growth factor; IGF-1, insulin-like growth factor-1; PDGF, platelet-derived growth factor; RASSF1A, Ras-association domain family 1; VEGF, vascular endothelial growth factor

From Murthy & Testa (1999), Altomare *et al.* (2005), Catalano *et al.* (2005), Kratzke & Gazdar (2005), Cacciotti *et al.* (2006), NIOSH (2009)

regulatory genes as well as inflammation-associated genes and apoptosis-related genes (Tsou *et al.*, 2007; Christensen *et al.*, 2008). Christensen *et al.* (2009) hypothesized that hypermethylation of specific genes confers a selective survival advantage to preneoplastic mesothelial cells in a microenvironment of persistent tissue injury and/or oxidative stress associated with exposure to asbestos fibres.

In summary, these new genomic and proteomics approaches offer promise for the discovery of novel biomarkers associated with the development of diffuse malignant mesothelioma following exposure to asbestos or erionite. No specific marker is yet available to identify those cancers.

4.3 Mechanisms of carcinogenesis

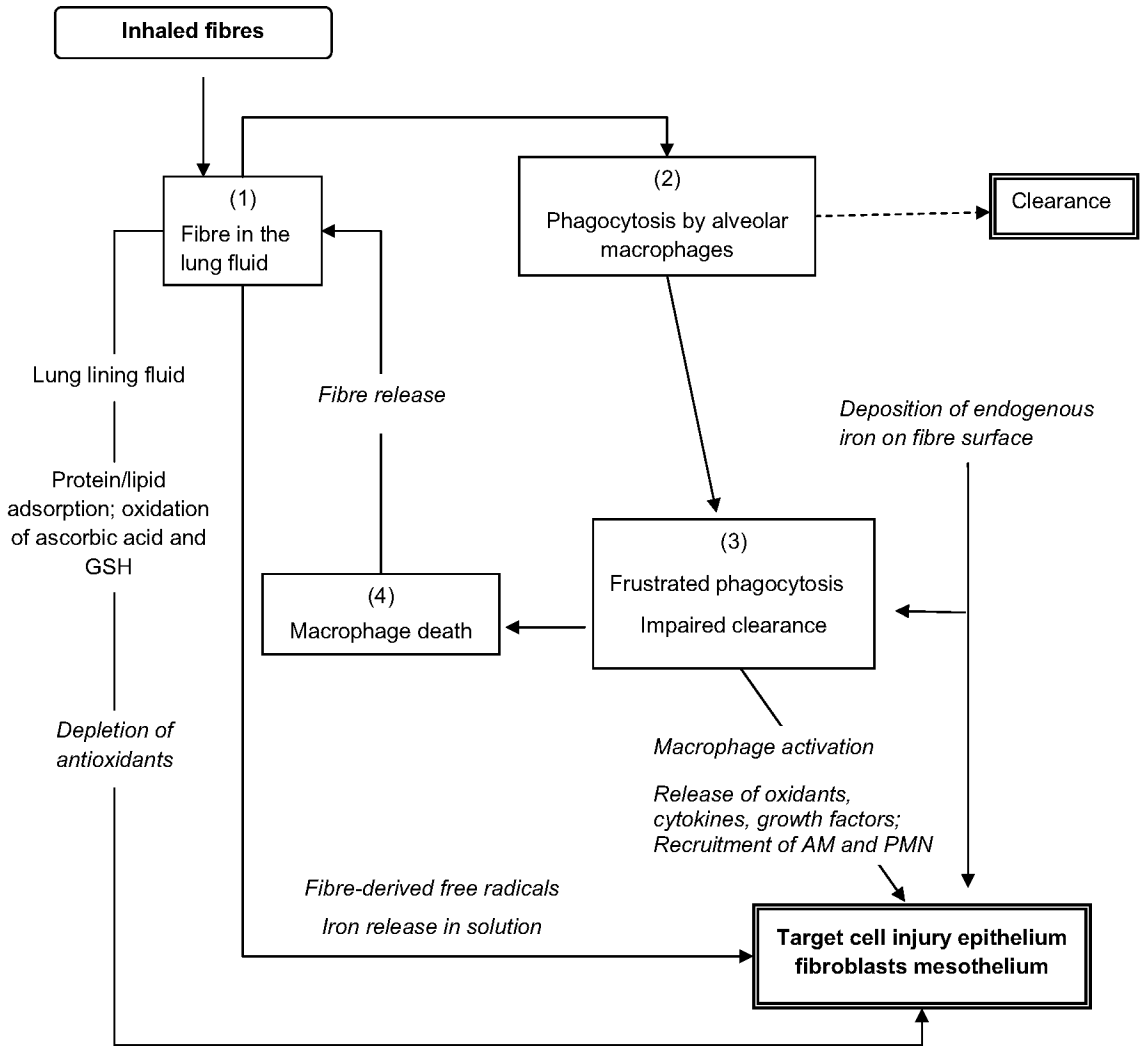
4.3.1 Physicochemical properties of mineral fibres associated with toxicity

Asbestos are natural fibrous silicates, with similar chemical composition (silica framework includes various metal cations, typically Mg^{2+}, Ca^{2+}, $Fe^{2+/3+}$, Na^{+}) mostly differing in the crystallographic constraints that yield the fibrous habit. They are poorly soluble minerals which only undergo selective leaching and incongruent dissolution. Erionite is a zeolite, which often crystallizes in thin long fibres. Major determinants of toxicity are form and size of the fibres, surface chemistry, and biopersistence. Crystal structure, chemical composition, origin, and associated minerals, as well as trace contaminants, modulate surface chemistry; and transformation, translocation, and solubility of the fibres in body fluids influence their biopersistence, a factor which modulates cumulative exposure (Fubini, 1997; Bernstein *et al.*, 2005; Fubini & Fenoglio, 2007; Sanchez *et al.*, 2009; Fig. 4.1).

(a) Crystal structure

Asbestos minerals can be divided into two groups: serpentine asbestos (chrysotile [$Mg_3Si_2O_5(OH)_4$]), and amphibole asbestos (crocidolite [$Na_2(Mg,Fe^{2+})_3Fe_2^{3+}Si_8O_{22}(OH)_2$], amosite [$(Mg,Fe^{2+})_7Si_8O_{22}(OH)_2$], tremolite [$Ca_2Mg_5Si_8O_{22}(OH)_2$], actinolite [$Ca_2(Mg,Fe^{2+})_5Si_8O_{22}(OH)_2$], and anthophyllite [$Mg_7Si_8O_{22}(OH)_2$]). Formulae reported are ideal and are always significantly modified in nature by the occurrence of several substituting cations (e.g. $Fe^{2+/3+}$, Al^{3+}, Na^{+}). The crystal structure of chrysotile results from the association of a tetrahedral silicate sheet of composition $(Si_2O_5)_n^{2n-}$ with an octahedral brucite-like sheet of composition $[Mg_3O_2(OH)_4]_n^{2n+}$, in which iron substitutes for magnesium. The two sheets are bonded to form a 1:1 layer silicate; a slight misfit between the sheets causes curling to form

Fig. 4.1 Physicochemical properties involved in the biological activity of asbestos fibres



AMs, alveolar macrophages; GSH, glutathione; PMNs, polymorphonuclear neutrophils
Adapted from Fubini & Otero Areán (1999), Fubini & Fenoglio (2007)

concentric cylinders, with the brucite-like layer on the outside. Van der Waals interparticle forces hold together fibrils into the actual fibre so that, when chrysotile breaks up, a large number of smaller fibres or fibrils are generated (Fubini & Otero Areán, 1999).

Amphiboles have an intrinsically elongated crystal structure which breaks up along planes within the crystal structure itself into progressively smaller fragments that generally retain a fibrous aspect. This structure can be described in terms of a basic structural unit formed by a double tetrahedral chain (corner-linked SiO_4 tetrahedra) of composition $(Si_4O_{11})_n^{6n-}$. These silicate double-chains share oxygen atoms with alternate layers of edge-sharing MO_6 octahedra, where M stands for a variety of cations: mostly Na^+, Mg^{2+}, Ca^{2+}, Fe^{2+}, or Fe^{3+} (Fubini & Otero Areán, 1999).

(b) *Form and size*

The pathogenic potential of asbestos depends upon its aspect ratio and fibre size. Fibre size affects respirability (respiratory zone falls off above aerodynamic diameters of 5 µm) and clearance by alveolar macrophages (section 4.1.1) (Donaldson & Tran, 2004). Short fibres are cleared more efficiently than longer ones, which undergo frustrated phagocytosis by macrophages. Short amosite fibres obtained by grinding long ones are less inflammogenic (Donaldson *et al.*, 1992), induce fewer chromosomal aberrations (Donaldson & Golyasnya, 1995), and reduce the inhibition of the pentose phosphate pathway (Riganti *et al.*, 2003). In-vitro genotoxicity studies demonstrated that both short and intermediate chrysotile asbestos fibres induced micronuclei formation and sister chromatid exchange in Chinese hamster lung cells. Intermediate fibres were more active than short fibres even when followed by treatment with dipalmitoyl lecithin, a principal constituent of pulmonary surfactant (Lu *et al.*, 1994). Long fibres but not short fibres of amosite asbestos, opsonized with rat immunoglobin, were shown to induce a dramatic enhancement of superoxide anions in macrophages isolated from rat lung (Hill *et al.*, 1995). Asbestos bodies are formed mostly on fibres longer than 20 µm (Roggli, 2004).

The role of the aspect ratio and size appears to be different for the three major asbestos-related diseases: i) asbestosis was reported as most closely associated with the surface area of retained fibres (NIOSH, 2009) although fibrosis also correlates with fibres > 2 µm long (Dodson *et al.*, 2003); ii) mesothelioma is better related to the numbers of fibres longer than about 5 µm and thinner than about 0.1 µm; and iii) lung cancer with fibres longer than about 10 µm and thicker than about 0.15 µm (NIOSH, 2009). Several studies, however, report the presence of very short fibres in lung and pleural tissue from patients with malignant mesothelioma (Dodson *et al.*, 2003; Dodson *et al.*, 2005; Suzuki *et al.*, 2005; Dodson *et al.*, 2007), suggesting caution to exclude short fibres (< 5 µm) in the development of asbestos-related diseases (Dodson *et al.*, 2003).

(c) *Surface reactivity*

In the last few decades, it has been accepted that, in addition to fibrous habit, surface reactivity also plays a role in the pathogenic effects of amphibole and chrysotile asbestos. The potential to release free radicals, among various other features, is considered the major determinant of the pathogenic response.

(i) *Free-radical generation*

Three different mechanisms of free-radical generation may take place at the surface of asbestos fibres, each one triggered by a different kind of active surface site: i) Fenton chemistry (yielding with H_2O_2 the generation of highly reactive hydroxyl radicals HO•); ii) Haber–Weiss cycle (in the absence of H_2O_2 and Fe(II), endogenous reductants allow progressive reduction of atmospheric oxygen to HO•); iii) homolytic

rupture of a carbon-hydrogen bond in biomolecules, with generation of carbon-centred radicals in the target molecule (peptides, proteins, etc.) (Hardy & Aust, 1995; Fubini & Otero Areán, 1999; Kamp & Weitzman, 1999).

Mechanism i) is relevant only in cellular compartments where H_2O_2 is present (i.e. phagolysosomal environment in macrophages), while Mechanisms ii) and iii)_may occur ubiquitously once fibres are inhaled. All mechanisms require the presence of iron ions. One stoichiometric chrysotile prepared by chemical synthesis, thus fully iron-free, was not active in free-radical generation (cell-free tests), did not induce lipid peroxidation, nor inhibit the pentose phosphate pathway in human lung epithelial cells, which is the opposite to what is found in natural specimens (Gazzano *et al.*, 2005). When loaded with less than 1 wt.% of Fe^{3+} the synthetic chrysotile also became active (Gazzano *et al.*, 2007). Asbestos fibres deprived of iron (following treatments with chelators) do not generate hydroxyl radicals (Fubini *et al.*, 1995) or damage DNA, and are less potent in causing lipid peroxidation *in vitro* (Hardy & Aust, 1995). However, not all iron ions are equally reactive in free-radical generation, depending upon their coordination and oxidation state (Shukla *et al.*, 2003; Bernstein *et al.*, 2005). Fe (II) is active even in trace amounts (Fubini *et al.*, 1995). Furthermore, Mechanism 3 requires isolated and poorly coordinated iron ions (Martra *et al.*, 2003; Turci *et al.*, 2007). The surface sites involved in this reaction are oxidized and become inactive following thermal treatments: amphibole asbestos fibres heated up to 400°C in air (Tomatis *et al.*, 2002) lose their potential in generating carboxyl radicals, but retain the reactivity for hydroxyl radicals, most likely through Mechanism 2, as long as their crystal structure is preserved. Conversely, the reduction of ferric into ferrous ions increases the radical activity (Gulumian *et al.*, 1993a). The radical yield appears unrelated to the total amount of iron (Gulumian *et al.*, 1993b), because chrysotile shows a similar behaviour to crocidolite in cell-free tests despite the lower content of iron (3–6% versus 27%). Iron oxides (magnetite, haematite) are unable to produce radical species, whereas model solids, e.g zeolites enriched with small amount of iron but with ions poorly coordinated and mostly in low valence state, are very reactive, particularly in hydrogen abstraction (Fubini *et al.*, 1995).

Iron-derived free radicals are believed to produce a variety of cell effects including lipid peroxidation (Ghio *et al.*, 1998; Gulumian, 1999), DNA oxidation (Aust & Eveleigh, 1999), TNF-release and cell apoptosis (Upadhyay & Kamp, 2003), adhesion (Churg *et al.*, 1998), and an increase of fibre uptake by epithelial cells (Hobson *et al.*, 1990).

(ii) Iron bioavailability and biodeposition

Iron can be removed from asbestos fibres by intracellular chelators. If iron is mobilized from low–molecular-weight chelators, e.g. citrate, redox activity may be altered. The chelator–iron complex can diffuse throughout the cell, and catalyse the formation of hydroxyl radicals. Mobilization of iron was shown to correlate with DNA strand breaks and with DNA oxidation induced by crocidolite, amosite, and chrysotile (Hardy & Aust, 1995). In human lung epithelial and pleural mesothelial cells, the extent of iron mobilization was also related to the inactivation of epidermal growth factor receptor (EGFR/ErbB1), a step in the pathway leading to apoptosis (Baldys & Aust, 2005).

Mineral fibres may also acquire iron which, under certain conditions, may modify their reactivity. Erionite (Dogan *et al.*, 2008) is able to bind both ferrous (through ion exchange) and ferric ions (through a precipitation or crystallization process). After ferrous-binding, erionite acquires the ability to generate hydroxyl radicals, and to catalyse DNA damage (DNA single-strand breaks); and after ferric-binding, the reactivity is acquired only in the presence of a reductant

(Hardy & Aust, 1995; Fach *et al.*, 2003; Ruda & Dutta, 2005). During their residence in the lung, asbestos fibres, like erionite fibres, acquire iron via a complex mechanism that may originate from the adsorption and disruption of ferritin, eventually yielding ferruginous bodies. These so-called asbestos bodies are preferentially formed onto long amphibole fibres but have also been found onto chrysotile fibres (Roggli, 2004). Although the presence of asbestos bodies in asbestos-related diseases is well documented, their biological role is still controversial. Iron deposition was thought to protect cells (Ghio *et al.*, 1997), but, deposited iron may become redox-active, thus enhancing the catalytic potential of the fibres (Ghio *et al.*, 2004). Asbestos bodies with amosite cores caused DNA single-strand breaks (Lund *et al.*, 1994); and increased radical damage to DNA was reported for ferritin-covered amosite in the presence of ascorbic acid (Otero-Areán *et al.*, 1999). Asbestos fibres might also disrupt normal iron homeostasis in the host by mobilizing and accumulating this metal (Ghio *et al.*, 2008).

Binding Fe (II) from solution increases iron mobilization from crocidolite by chelators, and induces DNA single-strand breaks. Increased lipid peroxidation and release of leukotriene B4 is found in alveolar macrophages from rats treated with Fe (III)-loaded crocidolite, and Fe (III)-loaded crocidolite fibres induce more DNA single-strand breaks *in vitro* than do untreated crocidolite fibres (Ghio *et al.*, 1992).

It was suggested that crocidolite stimulates inductible nitric oxide synthase by decreasing iron bioavailability (Aldieri *et al.*, 2001).

(d) Biopersistence, biodurability, and ecopersistence

The residence time in the lung depends upon both the clearance mechanisms and physico-chemical processes taking place. Clearance mechanisms are mainly related to the shape and size of the particle, whereas chemical composition, surface area, and structural parameters mainly affect leaching, dissolution, and breakage.

Selective leaching is more pronounced for serpentine asbestos than for amphiboles, which have no leachable "weak points" in their structure. Selective leaching of chrysotile occurs under strong acidic or chelating conditions, resulting in removal of Mg^{2+} ions. The kinetics vary according to the origin of the material, mechanical treatments, and associated contaminants, e.g. presence of nemalite (fibrous brucite) (Morgan, 1997). Chrysotile may lose magnesium *in vivo*, following phagocytosis by alveolar macrophages. The biological potential of magnesium-depleted chrysotile is greatly decreased (Langer & Nolan, 1994; Gulumian, 2005). Furthermore, leached fibres undergo breakage into shorter fibres, which may be cleared more readily from the lung. This accounts for the relatively low biopersistence of chrysotile compared to the amphiboles. The lungs of some chrysotile workers at autopsy contain low levels of chrysotile but substantial numbers of tremolite fibres, which is present in some chrysotile-bearing ores. For this reason, tremolite has been suggested to contribute to the carcinogenic effects seen in chrysotile miners (McDonald *et al.*, 1997; McDonald & McDonald, 1997; McDonald, 1998). Other asbestiform minerals may be associated with chrysotile, and, in some cases, modulate its toxicity, depending upon their amount and physicochemical characteristics. Balangeroite, occasionally intergrows with chrysotile (up to 5%) in the Balangero mine (Italy) and its sourroundings. Balangeroite fibres have a different structure from amphiboles, and are poorly eco- and bio-durable (Favero-Longo *et al.*, 2009; Turci *et al.*, 2009). Balangeroite may contribute to the overall toxicity of chrysotile, but it cannot be compared to tremolite nor considered to be solely responsible for the excess of mesothelioma found in Balangero (Mirabelli *et al.*, 2008).

In the natural environment, weathering processes carried out by micro-organisms

may induce chrysotile-leaching, contributing to its bioattenuation (Favero-Longo *et al.*, 2005). However, the dissolution of chrysotile is very low, because any breakdown of the silica framework takes place at a slow rate (Hume & Rimstidt, 1992), and is limited to a few layers in mild conditions (Gronow, 1987). Even in a strong acidic environment, the final product still retains a fibrous aspect at the nanoscale which is devoid of cations (Wypych *et al.*, 2005).

4.3.2 Direct genotoxicity

Mineral fibres may directly induce genotoxicity by catalysing the generation of reactive oxygen species resulting in oxidized DNA bases and DNA strand breaks that can produce gene mutations if not adequately repaired (IOM, 2006). Both asbestos and erionite fibres can induce DNA damage mediated by reactive oxygen species. Asbestos fibres have also been shown to physically interfere with the mitotic apparatus, which may result in aneuploidy or polyploidy, and specific chromosomal alterations characteristic of asbestos-related cancer (Jaurand, 1996).

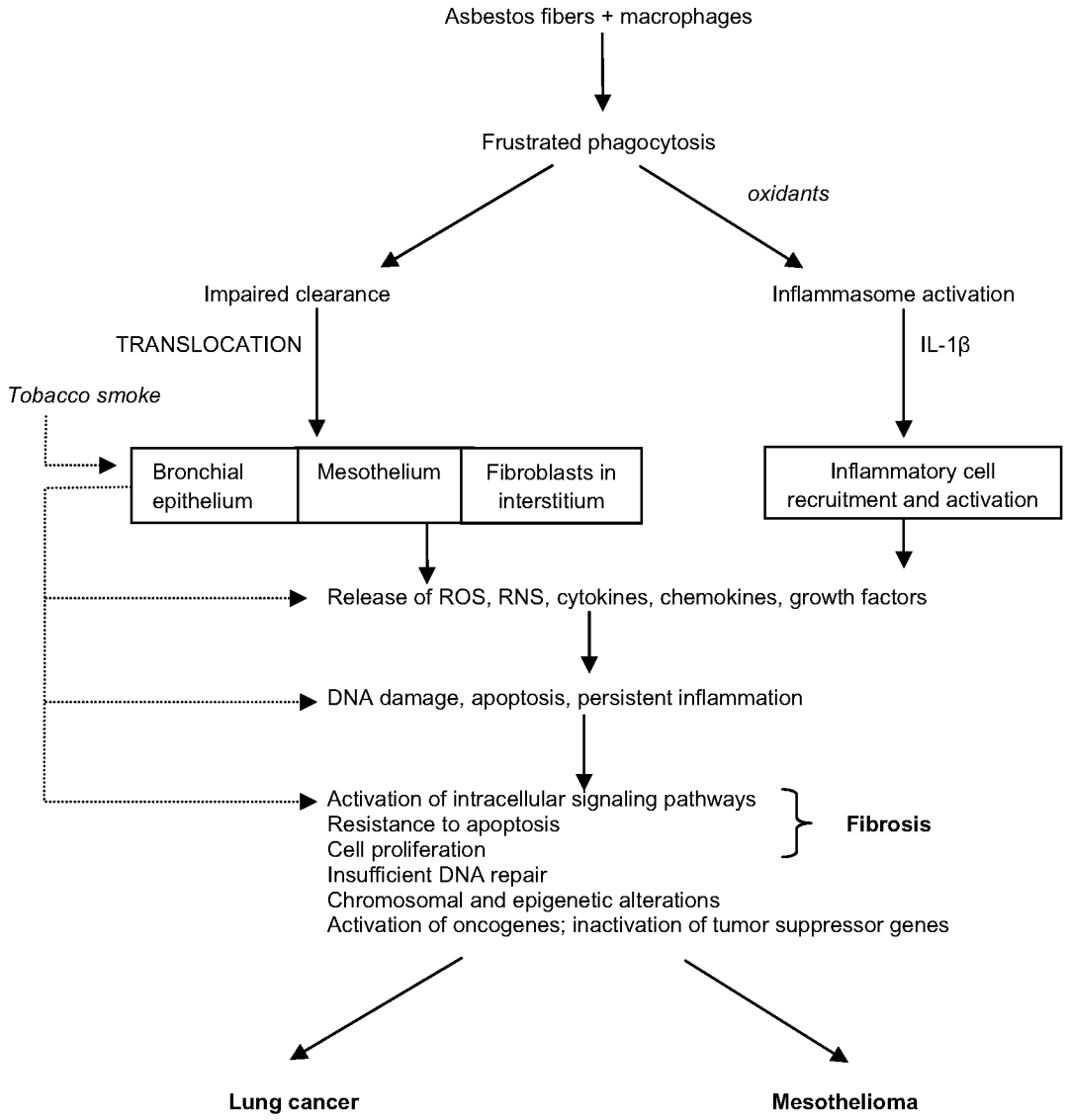
In addition to direct clastogenic and aneuploidogenic activities that may be induced following the translocation of asbestos fibres to target cell populations in the lungs, persistent inflammation and macrophage activation can secondarily generate additional reactive oxygen species, and reactive nitrogen species that can indirectly induce genotoxicity in addition to activation of intracellular signalling pathways, stimulation of cell proliferation and survival, and induction of epigenetic alterations (Fig. 4.2).

4.3.3 Indirect mechanisms

Asbestos fibres have unique and potent effects on alveolar macrophages that have been postulated to trigger the chain of events leading to chronic lung fibrosis (asbestosis), and lung cancer (Shukla *et al.*, 2003). Macrophages express a variety of cell-surface receptors that bind to mineral fibres leading to phagocytosis, macrophage apoptosis, or macrophage activation. Receptors expressed by macrophages and other target cells in the lung that bind mineral fibres include MARCO, a scavenger receptor class A, and integrin receptors (Boylan *et al.*, 1995; Gordon *et al.*, 2002; Arredouani *et al.*, 2005). Macrophage apoptosis has also been postulated to contribute to an increased incidence of autoimmune diseases in residents in Libby, Montana, USA, who are exposed to vermiculite contaminated with amphibole asbestos fibres (Noonan *et al.*, 2006; Blake *et al.*, 2008).

Phagocytosis of asbestos fibres leads to the excess generation of reactive oxygen and nitrogen species by both direct (described in Sections 4.3.1 and 4.3.2), and indirect mechanisms (Manning *et al.*, 2002). Alveolar macrophages phagocytize particulate materials and micro-organisms leading to assembly of NADPH oxidase in the phagolysosomal membrane that generates reactive oxygen species, which are potent antimicrobial agents. Asbestos fibres have elevated surface reactivity and redox-active iron that can generate hydroxyl radicals leading to lipid peroxidation, protein oxidation, and DNA damage resulting in lung injury that is amplified by persistent inflammation (Fig. 4.1 and 4.2). Recent investigations in genetically engineered mice have provided evidence for a key role of the NALP3 inflammasome as an intracellular sensor of the initial interactions between asbestos fibres and other crystals such as monosodium urate with macrophages (Yu & Finlay, 2008). The NALP3 inflammasome activates caspase-1 that cleaves IL-1β precursor to active IL-1β that is rapidly secreted (Cassel *et al.*, 2008; Dostert *et al.*, 2008). This cytokine then triggers the recruitment and activation of additional inflammatory cells and the release of additional cytokines including TNF-α, IL-6, and IL-8 that perpetuate a prolonged inflammatory response to these biopersistent mineral dusts (Shukla *et al.*, 2003).

Fig. 4.2 Proposed mechanism for the carcinogenicity of asbestos fibres



IL-1β, interleukin -1β; RNS, reactive nitrogen species; ROS, reactive oxygen species.
Adapted from Shukla *et al.* (2003), Kane (2006), Nymark *et al.* (2008)

The generation of reactive oxygen species by asbestos fibres has also been associated with inducing apoptosis in mesothelial cells (Broaddus *et al.*, 1996), and alveolar epithelial cells (Aljandali *et al.*, 2001).

Asbestos fibres have been shown to contribute to the transformation of a variety of target cells from different species *in vitro*, and to induce lung tumours and malignant pleural mesothelioma in rodents following chronic inhalation (Bernstein *et al.*, 2005). There are important species differences in the induction of asbestos-related cancers: rats are more susceptible to the induction of lung cancer, and hamsters are resistant to the induction of lung cancer but more susceptible to the development of malignant pleural mesothelioma (IARC, 2002). Subchronic inhalation studies using refractory ceramic fibres (RCF-1) suggest that the increased susceptibility of hamsters to developing malignant pleural mesothelioma may be related to greater translocation and accumulation of fibres in the pleural space, and an increased mesothelial cell proliferation in hamsters compared to rats (Gelzleichter *et al.*, 1999). There are serious limitations in extrapolating these species differences to humans. First, most human lung cancers, even in asbestos-exposed individuals, are confounded by tobacco smoke that has potent independent genotoxic effects as reviewed later in Section 4.4.1. Second, diffuse malignant mesothelioma in humans is usually diagnosed at an advanced stage, and there are no reliable premalignant changes or biomarkers that may provide clues about the molecular pathogenesis of mesothelioma associated with exposure to asbestos or erionite fibres (NIOSH, 2009).

A unifying mechanism based on the experimental in-vitro cellular and in-vivo rodent models is proposed in Fig. 4.2.

Recent biochemical studies have confirmed that oxidative damage to cytosine is a plausible biological mechanism leading to epigenetic alterations and development of cancer in association with persistent inflammation (Valinluck & Sowers, 2007). Neutrophils and macrophages are the source of reactive oxygen and nitrogen species triggered by phagocytosis of crystalline silica (quartz) or asbestos fibres. In addition, myeloperoxidase catalyses the formation of hypochlorous acid (HOC1) in neutrophils, and a specific peroxidase catalyses the formation of hypobromous acid (HOBr) in eosinophils (Babior, 2000). The formation of 8-oxoguanine, 5-hydroxymethylcytosine, or 5-hydroxycytosine interferes with DNA methylation and binding of methyl-CpG binding domains (MBDs). In contrast, chlorination or bromination of cytosine mimics 5-methylcytosine and induces heritable DNA methylation at previously unmethylated sites. Halogenated cytosines are also recognized by MBDs to facilitate chromatin remodelling. However, these modified bases are not recognized by DNA glycosylase, and are not repaired (Valinluck & Sowers, 2007).

This hypothesis linking heritable alterations in patterns of cytosine methylation with endogenous sources of oxidants released from inflammatory cells is a plausible explanation for the development of lung cancer and diffuse malignant mesothelioma associated with exposure to mineral fibres. Elevated neutrophils and eosinophils have been found in the pleural space following the inhalation of refractory ceramic fibres by hamsters and rats (Gelzleichter *et al.*, 1999). Furthermore, myeloperoxidase activity has been detected in rodent lungs following exposure to asbestos fibres, whereas a decreased lung inflammation was observed in asbestos-exposed myeloperoxidase-null mice (Haegens *et al.*, 2005). This indirect mechanism secondary to persistent inflammation may be responsible for altered epigenetic methylation profiles, which are characteristic of human malignant pleural mesotheliomas (Christensen *et al.*, 2009).

4.4 Susceptible populations

Both exogenous environmental and occupational exposures and endogenous factors including genetic susceptibility contribute to the development of lung cancer (NIOSH, 2009) and diffuse malignant mesothelioma (Weiner & Neragi-Miandoab, 2009). The best example of an exogenous exposure that is a major cofactor with asbestos fibres in the development of cancer of the larynx and of the lung is tobacco smoking (Table 4.3; Table 4.4; IARC, 2004; IOM, 2006). Additional environmental and occupational exposures are also risk factors for cancer of the larynx (Table 4.3) and of the lung (Table 4.4); these exposures are potential confounders in human epidemiological studies (IOM, 2006). Specific examples of these cofactors and other environmental and occupational exposures will be described in relationship to mechanisms of these cancers associated with mineral dust exposures.

4.4.1 *Other risk factors for cancer of the lung and of the larynx, and diffuse malignant mesothelioma*

(a) Tobacco smoke

Co-exposure to tobacco smoke and asbestos fibres is at least additive and possibly multiplicative in the development of lung cancer (Vainio & Boffetta, 1994). The inhalation of tobacco smoke (Walser *et al.*, 2008) as well as mineral fibres is associated with excess generation of reactive oxygen and nitrogen metabolites, cell injury and apoptosis, and persistent lung inflammation (Shukla *et al.*, 2003; IARC, 2004). Excess oxidant generation has been shown to enhance the penetration of asbestos fibres into respiratory epithelial cells, and to impair fibre clearance (McFadden *et al.*, 1986; Churg *et al.*, 1989), as well as altering the metabolism and detoxification of tobacco smoke carcinogens (Nymark *et al.*, 2008). Asbestos fibres can also adsorb tobacco smoke carcinogens and metals and facilitate their transport into the lungs (IOM, 2006). Asbestos fibres have also been shown to activate growth-factor receptors and cell-signalling pathways that stimulate cell proliferation and promote cell survival (Albrecht *et al.*, 2004). In summary, co-exposures to tobacco smoke and mineral fibres can amplify acquired genetic mutations induced by tobacco smoke carcinogens, and amplify cell proliferation in response to tissue injury leading to an increased risk for the development of cancer of the larynx and of the lung (Nymark *et al.*, 2008).

Table 4.3 Risk factors for the development of cancer of the larynx

Exposure	Reference
Active tobacco smoking	IARC (1986, 2004, 2012d)
Alcohol	IARC (1988, 2010, 2012d)
Mustard gas	IARC (1987a, 2012e)
Inorganic acid mists containing sulfuric acid	IARC (1992, 2012e)
Asbestos fibres	IOM (2006), IARC (2012b)
Human papilloma virus (HPV): types 6, 11, 16, 18 limited evidence	IARC (2007, 2012c)

Compiled by the Working Group

(b) Other occupational and environmental exposures

Alcohol and occupational exposure to irritants (Table 4.3) also contribute to the development of cancer of the larynx. These irritants, similar to inhalation of tobacco smoke, can cause repeated episodes of injury to the respiratory epithelium, resulting in metaplasia and dysplasia (Olshan, 2006); these preneoplastic lesions may then acquire additional molecular alterations and progress towards the development of invasive lung or laryngeal carcinoma. Other occupational exposures responsible for the development of lung cancer include direct-acting carcinogens such as ionizing radiation (IARC, 2000, 2012a), and metals (reviewed in IARC, 2012b).

Table 4.4 Risk factors for the development of cancer of the lung

Exposure	Reference
Active and passive tobacco smoking	IARC (2004, 2012d)
Ionizing radiation	IARC (2000, 2012a)
Respirable dusts and fibres:	
Asbestos	IARC (1987a, 2012b)
Talc containing asbestiform fibres	IARC (1987a, 2012b)
Erionite	IARC (1987a, 2012b)
Crystalline silica (quartz)	IARC (1997, 2012b)
Vermiculite contaminated with asbestos fibres	Amandus & Wheeler (1987), McDonald *et al.* (2004), IARC (2012b)
Bis(chloromethyl)ether and chloromethyl methyl ether	IARC (1987a, 2012c)
Arsenic and arsenic compounds	IARC (1987a, 2012b)
Beryllium	IARC (1993, 2012b)
Cadmium and cadmium compounds	IARC (1993, 2012b)
Hexavalent chromium	IARC (1990, 2012b)
Nickel sulfate, oxides, and sulfides	IARC (1990, 2012b)
Soots	IARC (1985, 1987a, 2012e)

Compiled by the Working Group

The strongest risk factors associated with the development of diffuse malignant mesothelioma include environmental or occupational exposures to erionite, asbestos fibres, and talc or vermiculite contaminated with asbestos fibres (Table 4.5; NIOSH, 2009). It is unknown whether the carcinogenic effects of exposure to mixed dusts contaminated with asbestos fibres can be entirely attributed to the asbestos fibres or whether co-exposure to talc or vermiculite dusts potentiates the retention and/or biological activity of asbestos fibres *in vivo* (Davis, 1996). The occurrence of talc pneumoconiosis and its relationship to other mineral dust contaminants including quartz and tremolite was recently reviewed (IARC, 2010). In-vitro assays of talc cytotoxicity were also summarized (IARC, 2010). No experimental studies have been published assessing the cytotoxicity of vermiculite contaminated with asbestos fibres. A sample of the mixture of amphibole fibres associated with Libby vermiculite ore has been shown to induce cytotoxicity and oxidative stress in macrophages *in vitro* (Blake *et al.*, 2007).

(c) SV40 and HPV viruses

Two human DNA tumour viruses have been linked with an increased risk for cancer of the larynx (Table 4.3; high-risk subtypes of human papillomavirus (HPV)) and diffuse malignant mesothelioma (Table 4.5; Simian virus 40 (SV40)).

The evidence for HPV 16 in the development of cancer of the larynx has been evaluated as limited, although it has been implicated as an independent risk factor in the development of other squamous cell carcinomas arising in the head and neck region (IARC, 2007, 2012c).

The association between exposure to SV40 and asbestos fibres in the development of diffuse malignant mesothelioma is highly controversial (Butel & Lednicky, 1999; Gazdar *et al.*, 2002; Shah, 2004; IOM, 2006). SV40 is not an essential cofactor for the development of mesothelioma; for example, residents of the Cappadocian villages in Turkey have a very high risk for diffuse malignant mesothelioma but do not have evidence of SV40 exposure (Dogan *et al.*, 2006). Although there are several in-vitro mechanistic

Table 4.5 Risk factors for the development of diffuse malignant mesothelioma

Exposure	Reference
Asbestos fibres	IARC (1987a, 2012b)
Erionite	IARC (1987a, 2012b)
Talc containing asbestiform fibres	IARC (1987a, 2012b)
Vermiculite contaminated with asbestos fibres	Amandus & Wheeler (1987), IARC (1987a, 2012e), McDonald *et al.* (2004)
Thorotrast	IARC (2001, 2012a)

Compiled by the Working Group

studies that support a role for SV40 viral oncogenes in the transformation of mesothelial cells, the human epidemiological evidence is inconclusive to support a causal association (Weiner & Neragi-Miandoab, 2009).

4.4.2 Genetic susceptibility

(a) Cancer of the lung

Tobacco smoke is the major cause of cancer of the lung; however, only a few rare hereditary syndromes are associated with an increased risk of lung, as well as other cancers: Bloom syndrome, Li-Fraumeni syndrome, and hereditary retinoblastoma (Lindor *et al.*, 2006). Other genetic polymorphisms in genes related to the metabolism and detoxification of tobacco smoke carcinogens, antioxidant defenses, and DNA repair have been suggested as predisposing factors for the development of lung cancer, although individually they contribute minimally to an increased risk (IOM, 2006). Attempts have been made to identify genetic polymorphisms in enzymes involved in xenobiotic metabolism and antioxidant defense that increase the risk for asbestos-related lung cancer; however, no consistent associations have been found (Nymark *et al.*, 2008).

(b) Diffuse malignant mesothelioma

With the exception of certain populations who have been exposed environmentally to asbestos or erionite fibres since birth (NIOSH, 2009), the development of diffuse malignant mesothelioma even in occupationally exposed workers is less common than the development of lung cancer (Nymark *et al.*, 2008). This observation has led to the hypothesis that there may be a genetic predisposition to the development of diffuse malignant mesothelioma following exposure to asbestos or erionite fibres. Isolated case reports provide examples of diffuse malignant mesothelioma in patients with neurofibromatosis type 2 (Baser *et al.*, 2002) or Li-Fraumeni syndrome (Heineman *et al.*, 1996) who are also exposed to asbestos. Several reports of familial cases of diffuse malignant mesothelioma are complicated by a common household exposure history (Weiner & Neragi-Miandoab, 2009). The strongest association between environmental exposure to erionite and genetic susceptibility to diffuse malignant mesothelioma has been provided by pedigree analysis of residents in the Cappadocia region of Turkey (Dogan *et al.*, 2006). However, there is skepticism about the accuracy of this analysis, and a recent review indicated that familial clusters can account for only 1.4% of cases of mesothelioma in Italy between 1978–2005 (Ascoli *et al.*, 2007; Ugolini *et al.*, 2008). One study has reported an association between genetic polymorphisms in the X-ray complementing group 1 gene (XRCC1) and the development of malignant mesothelioma in a population exposed to asbestos fibres (Dianzani *et al.*, 2006). More sensitive genome-wide association studies may uncover new markers for genetic susceptibility that predict increase risks of developing diffuse malignant mesothelioma following exposure to asbestos or erionite fibres.

4.5 Synthesis

The mechanistic basis for asbestos carcinogenicity is a complex interaction between crystalline mineral fibres and target cells *in vivo*. The most important physicochemical properties of asbestos fibres related to pathogenicity are surface chemistry and reactivity, surface area, fibre dimensions, and biopersistence. Multiple direct and indirect mechanisms have been proposed based on numerous in-vitro cellular assays, and acute and subchronic animal bioassays. These complex mechanisms most likely interact at multiple stages during the development of lung cancer and diffuse malignant mesothelioma.

The following general mechanisms have been proposed for the carcinogenicity of asbestos fibres (Fig. 4.1; Fig. 4.2):

1. Direct interaction between asbestos fibres and target cells *in vitro*:
   - Asbestos and erionite fibres have been shown to generate free radicals that directly induce genotoxicity as assessed by DNA breaks and oxidized bases in DNA.
   - Asbestos fibres have also been shown to interfere with the mitotic apparatus by direct physical interaction resulting in aneuploidy and polyploidy.
2. Indirect mechanisms:
   - In laboratory animals, asbestos fibres have been shown to induce macrophage activation and persistent inflammation that generate reactive oxygen and nitrogen species contributing to tissue injury, genotoxicity, and epigenetic alterations. Persistent inflammation and chronic oxidative stress have been associated with the activation of intracellular signalling pathways, resistance to apoptosis, and stimulation of cell proliferation.

There are significant species differences in the responses of the respiratory tract to the inhalation of asbestos fibres. The biological mechanisms responsible for these species differences are unknown. Based on comparative animal experimental studies, there may be differences in deposition and clearance of fibres in the lungs, in severity of fibrosis, in kinetics of translocation of fibres to the pleura, and in levels or types of antioxidant defense mechanisms.

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of all forms of asbestos (chrysotile, crocidolite, amosite, tremolite, actinolite, and anthophyllite). Asbestos causes mesothelioma and cancer of the lung, larynx, and ovary. Also positive associations have been observed between exposure to all forms of asbestos and cancer of the pharynx, stomach, and colorectum. For cancer of the colorectum, the Working Group was evenly divided as to whether the evidence was strong enough to warrant classification as *sufficient*.

There is *sufficient evidence* in experimental animals for the carcinogenicity of all forms of asbestos (chrysotile, crocidolite, amosite, tremolite, actinolite and anthophyllite).

All forms of asbestos (chrysotile, crocidolite, amosite, tremolite, actinolite and anthophyllite) are *carcinogenic to humans (Group 1).*

References

ACGIH (2007). Documentation of the TLVs and BEIs with Other Worldwide Occupational Exposure Values - 2007, Cincinnati, OH [CD-ROM]

Acheson ED, Gardner MJ, Pippard EC, Grime LP (1982). Mortality of two groups of women who manufactured gas masks from chrysotile and crocidolite asbestos: a 40-year follow-up. *Br J Ind Med*, 39: 344–348. PMID:6291580

Addison J & Davies LS (1990). Analysis of amphibole asbestos in chrysotile and other minerals. *Ann Occup Hyg*, 34: 159–175. doi:10.1093/annhyg/34.2.159 PMID:2169219

Albin M, Jakobsson K, Attewell R *et al.* (1990). Mortality and cancer morbidity in cohorts of asbestos cement workers and referents. *Br J Ind Med*, 47: 602–610. PMID:2207031

Albin M, Magnani C, Krstev S *et al.* (1999). Asbestos and cancer: An overview of current trends in Europe. *Environ Health Perspect*, 107: Suppl 2289–298. PMID:10350513

Albrecht C, Borm PJ, Unfried K (2004). Signal transduction pathways relevant for neoplastic effects of fibrous and non-fibrous particles. *Mutat Res*, 553: 23–35. PMID:15288530

Aldieri E, Ghigo D, Tomatis M *et al.* (2001). Iron inhibits the nitric oxide synthesis elicited by asbestos in murine macrophages. *Free Radic Biol Med*, 31: 412–417. doi:10.1016/S0891-5849(01)00612-8 PMID:11461780

Aliyu OA, Cullen MR, Barnett MJ *et al.* (2005). Evidence for excess cancer of the colorectum incidence among asbestos-exposed men in the Beta-Carotene and Retinol Efficacy Trial. *Am J Epidemiol*, 162: 868–878. doi:10.1093/aje/kwi285 PMID:16177148

Aljandali A, Pollack H, Yeldandi A *et al.* (2001). Asbestos causes apoptosis in alveolar epithelial cells: role of iron-induced free radicals. *J Lab Clin Med*, 137: 330–339. doi:10.1067/mlc.2001.114826 PMID:11329530

Altomare DA, Vaslet CA, Skele KL *et al.* (2005). A mouse model recapitulating molecular features of human mesothelioma. *Cancer Res*, 65: 8090–8095. doi:10.1158/0008-5472.CAN-05-2312 PMID:16166281

Amandus HE & Wheeler R (1987). The morbidity and mortality of vermiculite miners and millers exposed to tremolite-actinolite: Part II. Mortality. *Am J Ind Med*, 11: 15–26. doi:10.1002/ajim.4700110103 PMID:3028136

Amandus HE, Wheeler R, Jankovic J, Tucker J (1987). The morbidity and mortality of vermiculite miners and millers exposed to tremolite-actinolite: Part I. Exposure estimates. *Am J Ind Med*, 11: 1–14. doi:10.1002/ajim.4700110102 PMID:3028135

Anderson HA, Lilis R, Daum SM *et al.* (1976). Household-contact asbestos neoplastic risk. *Ann N Y Acad Sci*, 271: 1 Neoplasia in311–323. doi:10.1111/j.1749-6632.1976.tb23127.x PMID:1069520

Apostolou S, Balsara BR, Testa JR *et al.* (2006). *Cytogenetics of malignant mesothelioma.* In: *Malignant Mesothelioma: Advances in Pathogenesis, Diagnosis and Translational Therapies.* New York: Springer Science & Business Media, Inc., pp. 101–111.

Arredouani MS, Palecanda A, Koziel H *et al.* (2005). MARCO is the major binding receptor for unopsonized particles and bacteria on human alveolar macrophages. *J Immunol*, 175: 6058–6064. PMID:16237101

Ascoli V, Cavone D, Merler E *et al.* (2007). Mesothelioma in blood related subjects: report of 11 clusters among 1954 Italy cases and review of the literature. *Am J Ind Med*, 50: 357–369. doi:10.1002/ajim.20451 PMID:17407142

ATSDR (2001). Toxicological Profile for Asbestos (TP-61). US Dept. of Health & Human Services.

Aust AE & Eveleigh JF (1999). Mechanisms of DNA oxidation. *Proc Soc Exp Biol Med*, 222: 246–252. doi:10.1046/j.1525-1373.1999.d01-141.xPMID:10601883

Babior BM (2000). Phagocytes and oxidative stress. *Am J Med*, 109: 33–44. doi:10.1016/S0002-9343(00)00481-2 PMID:10936476

Baldys A & Aust AE (2005). Role of iron in inactivation of epidermal growth factor receptor after asbestos treatment of human lung and pleural target cells. *Am J Respir Cell Mol Biol*, 32: 436–442. doi:10.1165/rcmb.2004-0133OC PMID:15626777

Baris I, Simonato L, Artvinli M *et al.* (1987). Epidemiologicalal and environmental evidence of the health effects of exposure to erionite fibres: a four-year study in the Cappadocian region of Turkey. *Int J Cancer*, 39: 10–17. doi:10.1002/ijc.2910390104 PMID:3025107

Baris YI & Grandjean P (2006). Prospective study of mesothelioma mortality in Turkish villages with exposure to fibrous zeolite. *J Natl Cancer Inst*, 98: 414–417. doi:10.1093/jnci/djj106 PMID:16537834

Baser ME, De Rienzo A, Altomare D *et al.* (2002). Neurofibromatosis 2 and malignant mesothelioma. *Neurology*, 59: 290–291. PMID:12136076

Bégin R, Gauthier JJ, Desmeules M, Ostiguy G (1992). Work-related mesothelioma in Québec, 1967–1990. *Am J Ind Med*, 22: 531–542. doi:10.1002/ajim.4700220408 PMID:1332466

Berman DW & Crump KS (2008a). A meta-analysis of asbestos-related cancer risk that addresses fibre size and mineral type. *Crit Rev Toxicol*, 38: Suppl 149–73. doi:10.1080/10408440802273156 PMID:18686078

Berman DW & Crump KS (2008b). Update of potency factors for asbestos-related lung cancer and mesothelioma. *Crit Rev Toxicol*, 38: Suppl 11–47. doi:10.1080/10408440802276167 PMID:18671157

Bernstein D, Castranova V, Donaldson K *et al.* (2005). Testing of fibrous particles: short-term assays and strategies. *Inhal Toxicol*, 17: 497–537. PMID:16040559.

Berrino F, Richiardi L, Boffetta P *et al.* Milan JEM Working Group (2003). Occupation and larynx and hypopharynx cancer: a job-exposure matrix approach in an international case–control study in France, Italy, Spain and Switzerland. *Cancer Causes Control*, 14: 213–223. doi:10.1023/A:1023661206177 PMID:12814200

Berry G (1999). Models for mesothelioma incidence following exposure to fibres in terms of timing and duration of exposure and the biopersistence of the fibres. *Inhal Toxicol*, 11: 111–130. doi:10.1080/089583799197203 PMID:10380162

Berry G, Newhouse ML, Wagner JC (2000). Mortality from all cancers of asbestos factory workers in east London 1933–80. *Occup Environ Med*, 57: 782–785. doi:10.1136/oem.57.11.782 PMID:11024203

Bertolotti M, Ferrante D, Mirabelli D *et al.* (2008). Mortality in the cohort of the asbestos cement workers in the Eternit plant in Casale Monferrato (Italy) *Epidemiol Prev*, 32: 218–228. PMID:19186504

Blake DJ, Bolin CM, Cox DP *et al.* (2007). Internalization of Libby amphibole asbestos and induction of oxidative stress in murine macrophages. *Toxicol Sci*, 99: 277–288. doi:10.1093/toxsci/kfm166 PMID:17578862

Blake DJ, Wetzel SA, Pfau JC (2008). Autoantibodies from mice exposed to Libby amphibole asbestos bind SSA/Ro52-enriched apoptotic blebs of murine macrophages. *Toxicology*, 246: 172–179. doi:10.1016/j.tox.2008.01.008 PMID:18295955

Blount AM (1991). Amphibole content of cosmetic and pharmaceutical talcs. *Environ Health Perspect*, 94: 225–230. doi:10.2307/3431315 PMID:1659533

Boutin C, Dumortier P, Rey F *et al.* (1996). Black spots concentrate oncogenic asbestos fibres in the parietal pleura. Thoracoscopic and mineralogic study. *Am J Respir Crit Care Med*, 153: 444–449. PMID:8542156

Boylan AM, Sanan DA, Sheppard D, Broaddus VC (1995). Vitronectin enhances internalization of crocidolite asbestos by rabbit pleural mesothelial cells via the integrin alpha v beta 5. *J Clin Invest*, 96: 1987–2001. doi:10.1172/JCI118246 PMID:7560092

Broaddus VC, Yang L, Scavo LM *et al.* (1996). Asbestos induces apoptosis of human and rabbit pleural mesothelial cells via reactive oxygen species. *J Clin Invest*, 98: 2050–2059. doi:10.1172/JCI119010 PMID:8903324

Bruno C, Comba P, Zona A (2006). Adverse health effects of fluoro-edenitic fibers: epidemiological evidence and public health priorities. *Ann N Y Acad Sci*, 1076: 778–783. doi:10.1196/annals.1371.020 PMID:17119254

Butel JS & Lednicky JA (1999). Cell and molecular biology of simian virus 40: implications for human infections and disease. *J Natl Cancer Inst*, 91: 119–134. doi:10.1093/jnci/91.13.1166a PMID:9923853

Cacciotti P, Mutti L, Gaudino G (2006). *Growth factors and malignant mesothelioma.* In: *Malignant Mesothelioma: Advances in Pathogenesis, Diagnosis and Translational Therapies.* Pass HI, Vogelzang NJ Carbone M, editors. New York: Springer Science & Business Media, Inc., pp. 112-123.

Camus M, Siemiatycki J, Meek B (1998). Nonoccupational exposure to chrysotile asbestos and the risk of lung cancer. *N Engl J Med*, 338: 1565–1571. doi:10.1056/NEJM199805283382201 PMID:9603793

Cantor KP (1997). Drinking water and cancer. *Cancer Causes Control*, 8: 292–308. doi:10.1023/A:1018444902486 PMID:9498894

Cassel SL, Eisenbarth SC, Iyer SS *et al.* (2008). The Nalp3 inflammasome is essential for the development of silicosis. *Proc Natl Acad Sci USA*, 105: 9035–9040. doi:10.1073/pnas.0803933105 PMID:18577586

Catalano A, Strizzi L, Procopio A (2005). *Angiogenesis and mesothelioma.* In: *Malignant Mesothelioma: Advances in Pathogenesis, Diagnosis and Translational Therapies.* Pass HI, Vogelzang NJ, Carbone M, editors. New York: Springer Science & Business Media, Inc., pp. 141-150.

Christensen BC, Godleski JJ, Marsit CJ *et al.* (2008). Asbestos exposure predicts cell cycle control gene promoter methylation in pleural mesothelioma. *Carcinogenesis*, 29: 1555–1559. doi:10.1093/carcin/bgn059 PMID:18310086

Christensen BC, Houseman EA, Godleski JJ *et al.* (2009). Epigenetic profiles distinguish pleural mesothelioma from normal pleura and predict lung asbestos burden and clinical outcome. *Cancer Res*, 69: 227–234. doi:10.1158/0008-5472.CAN-08-2586 PMID:19118007

Churg A, Hobson J, Berean K, Wright J (1989). Scavengers of active oxygen species prevent cigarette smoke-induced asbestos fibre penetration in rat tracheal explants. *Am J Pathol*, 135: 599–603. PMID:2801882

Churg A, Sun J, Zay K (1998). Cigarette smoke increases amosite asbestos fibre binding to the surface of tracheal epithelial cells. *Am J Physiol*, 275: L502–L508. PMID:9728044

Churg A & Warnock ML (1980). Asbestos fibres in the general population. *Am Rev Respir Dis*, 122: 669–678. PMID:7447151

Cocco P, Palli D, Buiatti E *et al.* (1994). Occupational exposures as risk factors for gastric cancer in Italy. *Cancer Causes Control*, 5: 241–248. doi:10.1007/BF01830243 PMID:8061172

Coffin DL, Cook PM, Creason JP (1992). Relative mesothelioma induction in rats by mineral fibres:comparison with residual pulmonary mineral fibre number and epidemiology. *Inhal Toxicol*, 4: 273–300. doi:10.3109/08958379209145671

Comba P, Gianfagna A, Paoletti L (2003). Pleural mesothelioma cases in Biancavilla are related to a new fluoro-edenite fibrous amphibole. *Arch Environ Health*, 58: 229–232. doi:10.3200/AEOH.58.4.229-232 PMID:14655903

Conforti PM, Kanarek MS, Jackson LA *et al.* (1981). Asbestos in drinking water and cancer in the San Francisco Bay Area: 1969–1974 incidence. *J Chronic Dis*, 34: 211–224. doi:10.1016/0021-9681(81)90065-5 PMID:7240361

Cullen MR (1996). The amphibole hypothesis of asbestos-related cancer–gone but not forgotten. *Am J Public Health*, 86: 158–159. doi:10.2105/AJPH.86.2.158 PMID:8633728

Cullen MR & Baloyi RS (1991). Chrysotile asbestos and health in Zimbabwe: I. Analysis of miners and millers compensated for asbestos-related diseases since independence (1980). *Am J Ind Med*, 19: 161–169. doi:10.1002/ajim.4700190204 PMID:1847001

Cullen RT, Searl A, Buchanan D *et al.*R. T.Cullen, A. Searl, D. Buchanan (2000). Pathogenicity of a special-purpose glass microfibre (E glass) relative to

another glass microfibre and amosite asbestos. *Inhal Toxicol*, 12: 959–977. doi:10.1080/08958370050138012 PMID:10989371

Davis1996). Mixed fibrous and non-fibrous dusts exposures and interactions between agents in fibre carcinogenesis. IARC Sci Pub, 140:127

Davis JM, Addison J, Bolton RE *et al.* (1985). Inhalation studies on the effects of tremolite and brucite dust in rats. *Carcinogenesis*, 6: 667–674. doi:10.1093/carcin/6.5.667 PMID:2988806

Davis JM, Addison J, Bolton RE *et al.* (1986a). Inhalation and injection studies in rats using dust samples from chrysotile asbestos prepared by a wet dispersion process. *Br J Exp Pathol*, 67: 113–129. PMID:3004552

Davis JM, Addison J, Bolton RE *et al.* (1986b). The pathogenicity of long versus short fibre samples of amosite asbestos administered to rats by inhalation and intraperitoneal injection. *Br J Exp Pathol*, 67: 415–430. PMID:2872911

Davis JM, Beckett ST, Bolton RE *et al.* (1978). Mass and number of fibres in the pathogenesis of asbestos-related lung disease in rats. *Br J Cancer*, 37: 673–688. PMID:656299

Davis JM, Beckett ST, Bolton RE, Donaldson K (1980a). The effects of intermittent high asbestos exposure (peak dose levels) on the lungs of rats. *Br J Exp Pathol*, 61: 272–280. PMID:7426382

Davis JM, Beckett ST, Bolton RE, Donaldson K (1980b). A comparison of the pathological effects in rats of the UICC reference samples of amosite and chrysotile with those of amosite and chrysotile collected from the factory environment. *IARC Sci Publ*, 30: 285–292. PMID:7239647

Davis JM, Bolton RE, Douglas AN *et al.* (1988). Effects of electrostatic charge on the pathogenicity of chrysotile asbestos. *Br J Ind Med*, 45: 292–299. PMID:2837270

Davis JM, Bolton RE, Miller BG, Niven K (1991b). Mesothelioma dose response following intraperitoneal injection of mineral fibres. *Int J Exp Pathol*, 72: 263–274. PMID:1843255

Davis JM, Brown DM, Cullen RT *et al.* (1996). A comparison of methods of determining and predicting pathogenicity of mineral fibres. *Inhal Toxicol*, 8: 747–770. doi:10.3109/08958379608995209

Davis JM & Jones AD (1988). Comparisons of the pathogenicity of long and short fibres of chrysotile asbestos in rats. *Br J Exp Pathol*, 69: 717–737. PMID:2848570

Davis JM, Jones AD, Miller BG (1991a). Experimental studies in rats on the effects of asbestos inhalation coupled with the inhalation of titanium dioxide or quartz. *Int J Exp Pathol*, 72: 501–525. PMID:1742204

Dement JM & Brown DP (1994). Lung cancer mortality among asbestos textile workers: a review and update. *Ann Occup Hyg*, 38: 525–532, 412. doi:10.1093/annhyg/38.4.525 PMID:7978974

Dement JM, Brown DP, Okun A (1994). Follow-up study of chrysotile asbestos textile workers: cohort mortality and case–control analyses. *Am J Ind Med*, 26: 431–447. doi:10.1002/ajim.4700260402 PMID:7810543

Dement JM, Kuempel ED, Zumwalde RD *et al.* (2008). Development of a fibre size-specific job-exposure matrix for airborne asbestos fibres. *Occup Environ Med*, 65: 605–612. doi:10.1136/oem.2007.033712 PMID:17984198

Demers RY, Burns PB, Swanson GM (1994). Construction occupations, asbestos exposure, and cancer of the colon and rectum. *J Occup Med*, 36: 1027–1031. PMID:7823215

Dianzani I, Gibello L, Biava A *et al.* (2006). Polymorphisms in DNA repair genes as risk factors for asbestos-related malignant mesothelioma in a general population study. *Mutat Res*, 599: 124–134. PMID:16564556

Dodson RF & Atkinson MA (2006). Measurements of asbestos burden in tissues. *Ann N Y Acad Sci*, 1076: 281–291. doi:10.1196/annals.1371.015 PMID:17119209

Dodson RF, Atkinson MA, Levin JL (2003). Asbestos fibre length as related to potential pathogenicity: a critical review. *Am J Ind Med*, 44: 291–297. doi:10.1002/ajim.10263 PMID:12929149

Dodson RF, Graef R, Shepherd S *et al.* (2005). Asbestos burden in cases of mesothelioma from individuals from various regions of the United States. *Ultrastruct Pathol*, 29: 415–433. doi:10.1080/019131290945682 PMID:16257868

Dodson RF, Shepherd S, Levin J, Hammar SP (2007). Characteristics of asbestos concentration in lung as compared to asbestos concentration in various levels of lymph nodes that collect drainage from the lung. *Ultrastruct Pathol*, 31: 95–133. doi:10.1080/01913120701423907 PMID:17613992

Dodson RF, Williams MG Jr, Corn CJ *et al.* (1990). Asbestos content of lung tissue, lymph nodes, and pleural plaques from former shipyard workers. *Am Rev Respir Dis*, 142: 843–847. PMID:2171386

Dogan AU, Baris YI, Dogan M *et al.* (2006). Genetic predisposition to fibre carcinogenesis causes a mesothelioma epidemic in Turkey. *Cancer Res*, 66: 5063–5068. doi:10.1158/0008-5472.CAN-05-4642 PMID:16707428

Dogan AU, Dogan M, Hoskins JA (2008). Erionite series minerals: mineralogical and carcinogenic properties. *Environ Geochem Health*, 30: 367–381. doi:10.1007/s10653-008-9165-x PMID:18347916

Doll R (1955). Mortality from lung cancer in asbestos workers. *Br J Ind Med*, 12: 81–86. PMID:14363586

Donaldson K & Golyasnya N (1995). Cytogenetic and pathogenic effects of long and short amosite asbestos. *J Pathol*, 177: 303–307. doi:10.1002/path.1711770313 PMID:8551393

Donaldson K, Li XY, Dogra S *et al.* (1992). Asbestos-stimulated tumour necrosis factor release from alveolar macrophages depends on fibre length and opsonization.

J Pathol, 168: 243–248. doi:10.1002/path.1711680214 PMID:1334143

Donaldson K & Tran CL (2004). An introduction to the short-term toxicology of respirable industrial fibres. *Mutat Res*, 553: 5–9. PMID:15288528

Dostert C, Pétrilli V, Van Bruggen R *et al.* (2008). Innate immune activation through Nalp3 inflammasome sensing of asbestos and silica. *Science*, 320: 674–677. doi:10.1126/science.1156995 PMID:18403674

Dumortier P, Coplü L, Broucke I *et al.* (2001). Erionite bodies and fibres in bronchoalveolar lavage fluid (BALF) of residents from Tuzköy, Cappadocia, Turkey. *Occup Environ Med*, 58: 261–266. doi:10.1136/oem.58.4.261 PMID:11245743

Dumortier P, De Vuyst P, Yernault JC (1989). Non-fibrous inorganic particles in human bronchoalveolar lavage fluids. *Scanning Microsc*, 3: 1207–1216, discussion 1217–1218. PMID:2561220

Edelman DA (1988). Exposure to asbestos and the risk of gastrointestinal cancer: a reassessment. *Br J Ind Med*, 45: 75–82. PMID:3342198

Enterline PE, Hartley J, Henderson V (1987). Asbestos and cancer: a cohort followed up to death. *Br J Ind Med*, 44: 396–401. PMID:3606968

Esteller M (2005). Dormant hypermethylated tumour suppressor genes: questions and answers. *J Pathol*, 205: 172–180. doi:10.1002/path.1707 PMID:15643671

EU (1999). Commission Directive 1999/77/EC of 26 July 1999. Official Journal of the European Communities. [L207/18 – L207/20]

EU (2003). Directive 2003/18/EC of the European Parliament and of the Council of 27 March 2003 amending Council Directive 83/477/EEC on the protection of workers from the risks related to exposure to asbestos at work. Official Journal L 097, 15/04/2003 P. 0048 – 0052.

Fach E, Kristovich R, Long JF *et al.* (2003). The effect of iron on the biological activities of erionite and mordenite. *Environ Int*, 29: 451–458. doi:10.1016/S0160-4120(02)00193-9 PMID:12705942

Favero-Longo SE, Turci F, Tomatis M *et al.* (2005). Chrysotile asbestos is progressively converted into a non-fibrous amorphous material by the chelating action of lichen metabolites. *J Environ Monit*, 7: 764–766. doi:10.1039/b507569f PMID:16049575

Favero-Longo SE, Turci F, Tomatis M *et al.* (2009). The effect of weathering on ecopersistence, reactivity, and potential toxicity of naturally occurring asbestos and asbestiform mineral. *J Toxicol Environ Health A*, 72: 305–314. PMID:19184746.

Feron VJ, Scherrenberg PM, Immel HR, Spit BJ (1985). Pulmonary response of hamsters to fibrous glass: chronic effects of repeated intratracheal instillation with or without benzo[a]pyrene. *Carcinogenesis*, 6: 1495–1499. doi:10.1093/carcin/6.10.1495 PMID:4042277

Ferrante D, Bertolotti M, Todesco A *et al.* (2007). Cancer mortality and incidence of mesothelioma in a cohort of wives of asbestos workers in Casale Monferrato, Italy. *Environ Health Perspect*, 115: 1401–1405. PMID:17938727

Finkelstein MM (1983). Mortality among long-term employees of an Ontario asbestos-cement factory. *Br J Ind Med*, 40: 138–144. PMID:6830709

Fredriksson M, Bengtsson NO, Hardell L, Axelson O (1989). Colon cancer, physical activity, and occupational exposures. A case–control study. *Cancer*, 63: 1838–1842. doi:10.1002/1097-0142(19900501)63:9<1838::AID-CNCR2820630930>3.0.CO;2-4 PMID:2702592

Frumkin H & Berlin J (1988). Asbestos exposure and gastrointestinal malignancy review and meta-analysis. *Am J Ind Med*, 14: 79–95. doi:10.1002/ajim.4700140110 PMID:3044065

Fubini B (1997). Surface reactivity in the pathogenic response to particulates. *Environ Health Perspect*, 105: Suppl 51013–1020. doi:10.2307/3433502 PMID:9400693

Fubini B & Fenoglio I (2007). Toxic potential of mineral dusts. *Elements*, 3: 407–414. doi:10.2113/GSELEMENTS.3.6.407

Fubini B, Mollo L, Giamello E (1995). Free radical generation at the solid/liquid interface in iron containing minerals. *Free Radic Res*, 23: 593–614. doi:10.3109/10715769509065280 PMID:8574353

Fubini B & Otero Areán C (1999). Chemical aspects of the toxicity of inhaled mineral dusts. *Chem Soc Rev*, 28: 373–381. doi:10.1039/a805639k

Gamble J (2008). Risk of gastrointestinal cancers from inhalation and ingestion of asbestos. *Regul Toxicol Pharmacol*, 52: SupplS124–S153. doi:10.1016/j.yrtph.2007.10.009 PMID:18078700

Garabrant DH, Peters RK, Homa DM (1992). Asbestos and colon cancer: lack of association in a large case–control study. *Am J Epidemiol*, 135: 843–853. PMID:1585897

Gardner MJ, Winter PD, Pannett B, Powell CA (1986). Follow up study of workers manufacturing chrysotile asbestos cement products. *Br J Ind Med*, 43: 726–732. PMID:3024695

Gazdar AF, Butel JS, Carbone M (2002). SV40 and human tumours: myth, association or causality? *Nat Rev Cancer*, 2: 957–964. doi:10.1038/nrc947 PMID:12459734

Gazzano E, Foresti E, Lesci IG *et al.* (2005). Different cellular responses evoked by natural and stoichiometric synthetic chrysotile asbestos. *Toxicol Appl Pharmacol*, 206: 356–364. doi:10.1016/j.taap.2004.11.021 PMID:16039947

Gazzano E, Turci F, Foresti E *et al.* (2007). Iron-loaded synthetic chrysotile: a new model solid for studying the role of iron in asbestos toxicity. *Chem Res Toxicol*, 20: 380–387. doi:10.1021/tx600354f PMID:17315889

Gelzleichter TR, Bermudez E, Mangum JB *et al.* (1999). Comparison of pulmonary and pleural responses of rats and hamsters to inhaled refractory ceramic fibres.

Toxicol Sci, 49: 93–101. doi:10.1093/toxsci/49.1.93 PMID:10367346

Gerhardsson de Verdier M, Plato N, Steineck G, Peters JM (1992). Occupational exposures and cancer of the colon and rectum. *Am J Ind Med*, 22: 291–303. doi:10.1002/ajim.4700220303 PMID:1519614

Germani D, Belli S, Bruno C *et al.* (1999). Cohort mortality study of women compensated for asbestosis in Italy. *Am J Ind Med*, 36: 129–134. doi:10.1002/(SICI)1097-0274(199907)36:1<129::AID-AJIM18>3.0.CO;2-9 PMID:10361597

Ghio AJ, Churg A, Roggli VL (2004). Ferruginous bodies: implications in the mechanism of fibre and particle toxicity. *Toxicol Pathol*, 32: 643–649. doi:10.1080/01926230490885733 PMID:15513907

Ghio AJ, Kadiiska MB, Xiang QH, Mason RP (1998). In vivo evidence of free radical formation after asbestos instillation: an ESR spin trapping investigation. *Free Radic Biol Med*, 24: 11–17. doi:10.1016/S0891-5849(97)00063-4 PMID:9436609

Ghio AJ, LeFurgey A, Roggli VL (1997). In vivo accumulation of iron on crocidolite is associated with decrements in oxidant generation by the fibre. *J Toxicol Environ Health*, 50: 125–142. doi:10.1080/009841097160537 PMID:9048957

Ghio AJ, Stonehuerner J, Richards J, Devlin RB (2008). Iron homeostasis in the lung following asbestos exposure. *Antioxid Redox Signal*, 10: 371–377. doi:10.1089/ars.2007.1909 PMID:17999626

Ghio AJ, Zhang J, Piantadosi CA (1992). Generation of hydroxyl radical by crocidolite asbestos is proportional to surface [Fe3+]. [Fe3+]*Arch Biochem Biophys*, 298: 646–650. doi:10.1016/0003-9861(92)90461-5 PMID:1329664

Gibbs AR, Stephens M, Griffiths DM *et al.* (1991). Fibre distribution in the lungs and pleura of subjects with asbestos related diffuse pleural fibrosis. *Br J Ind Med*, 48: 762–770. PMID:1659443

Gibbs GW & Hwang CY (1975). Physical parameters of airborne asbestos fibres in various work environments-preliminary findings. *Am Ind Hyg Assoc J*, 36: 459–466. PMID:1229888

Gibbs GW & Hwang CY (1980). Dimensions of airborne asbestos fibres. *IARC Sci Publ*, 30: 69–78. PMID:7239672

Glickman LT, Domanski LM, Maguire TG *et al.* (1983). Mesothelioma in pet dogs associated with exposure of their owners to asbestos. *Environ Res*, 32: 305–313. doi:10.1016/0013-9351(83)90114-7 PMID:6641667

Gloyne SR (1935). Two cases of squamous carcinoma of the lung occurring in asbestosis. *Tubercle*, 17: 5–10. doi:10.1016/S0041-3879(35)80795-2

Goldberg MS, Parent ME, Siemiatycki J *et al.* (2001). A case–control study of the relationship between the risk of colon cancer in men and exposures to occupational agents. *Am J Ind Med*, 39: 531–546. doi:10.1002/ajim.1052 PMID:11385637

Goldstein B & Coetzee FS (1990). Experimental malignant mesothelioma in baboons. Suid-Afrik. *Tydskrift voor Wetenskap*, 86: 89–93.

Goldstein B, Rendall RE, Webster I (1983). A comparison of the effects of exposure of baboons to crocidolite and fibrous-glass dusts. *Environ Res*, 32: 344–359. doi:10.1016/0013-9351(83)90117-2 PMID:6315390

Goodman M, Morgan RW, Ray R *et al.* (1999). Cancer in asbestos-exposed occupational cohorts: a meta-analysis. *Cancer Causes Control*, 10: 453–465. doi:10.1023/A:1008980927434 PMID:10530617

Gordon GJ, Jensen RV, Hsiao LL *et al.* (2002). Translation of microarray data into clinically relevant cancer diagnostic tests using gene expression ratios in lung cancer and mesothelioma. *Cancer Res*, 62: 4963–4967. PMID:12208747

Graham J & Graham R (1967). Ovarian cancer and asbestos. *Environ Res*, 1: 115–128. doi:10.1016/0013-9351(67)90008-4 PMID:5628974

Greillier L, Baas P, Welch JJ *et al.* (2008). Biomarkers for malignant pleural mesothelioma: current status. *Mol Diagn Ther*, 12: 375–390. PMID:19035624

Gronow JR (1987). The dissolution of asbestos fibres in water. *Clay Miner*, 22: 21–35. doi:10.1180/claymin.1987.022.1.03

Gross P, DeTreville RT, Tolker EB *et al.* (1967). Experimental asbestosis. The development of lung cancer in rats with pulmonary deposits of chrysotile asbestos dust. *Arch Environ Health*, 15: 343–355. PMID:6035084

Gulumian M (1999). The ability of mineral dusts and fibres to initiate lipid peroxidation. Part I: parameters which determine this ability. *Redox Rep*, 4: 141–163. doi:10.1179/135100099101534855 PMID:10658820

Gulumian M (2005). An update on the detoxification processes for silica particles and asbestos fibres: successess and limitations. *J Toxicol Environ Health B Crit Rev*, 8: 453–483. doi:10.1080/10937400590952547 PMID:16188731

Gulumian M, Bhoolia DJ, Du Toit RS *et al.* (1993a). Activation of UICC crocidolite: the effect of conversion of some ferric ions to ferrous ions. *Environ Res*, 60: 193–206. doi:10.1006/enrs.1993.1027 PMID:8386081

Gulumian M, Bhoolia DJ, Theodorou P *et al.* (1993b). Parameters Which Determine the Activity of the Transition-Metal Iron in Crocidolite Asbestos - Esr, Mossbauer Spectroscopic and Iron Mobilization Studies. *S Afr J Sci*, 89: 405–409.

Haegens A, van der Vliet A, Butnor KJ *et al.* (2005). Asbestos-induced lung inflammation and epithelial cell proliferation are altered in myeloperoxidase-null mice. *Cancer Res*, 65: 9670–9677. doi:10.1158/0008-5472.CAN-05-1751 PMID:16266986

Hagemeyer O, Otten H, Kraus T (2006). Asbestos consumption, asbestos exposure and asbestos-related occupational diseases in Germany. *Int Arch Occup*

Environ Health, 79: 613–620. doi:10.1007/s00420-006-0091-x PMID:16523318

Hardy JA & Aust AE (1995). Iron in asbestos chemistry and carcinogenicity. *Chem Rev*, 95: 97–118. doi:10.1021/cr00033a005

Health and Safety Executive (2005). *HSG 248 'Asbestos: The analysts' guide for sampling, analysis and clearance procedures'*. London: HSE Books.

Health Effects Institute (1991). *Asbestos in public and commercial buildings: A literature review and synthesis of current knowledge*. Cambridge, Massachusetts: Health Effects Institute-Asbestos Research.

Hein MJ, Stayner LT, Lehman E, Dement JM (2007). Follow-up study of chrysotile textile workers: cohort mortality and exposure-response. *Occup Environ Med*, 64: 616–625. doi:10.1136/oem.2006.031005 PMID:17449563

Heineman EF, Bernstein L, Stark AD, Spirtas R (1996). Mesothelioma, asbestos, and reported history of cancer in first-degree relatives. *Cancer*, 77: 549–554. doi:10.1002/(SICI)1097-0142(19960201)77:3<549::AID-CNCR18>3.0.CO;2-4 PMID:8630964

Heller DS, Gordon RE, Westhoff C, Gerber S (1996). Asbestos exposure and ovarian fibre burden. *Am J Ind Med*, 29: 435–439. doi:10.1002/(SICI)1097-0274(199605)29:5<435::AID-AJIM1>3.0.CO;2-L PMID:8732916

Hesterberg TW, Axten C, McConnell EE *et al.* T. W. Hesterberg, C. Axten, E. E. M (1999). Studies on the inhalation toxicology of two fibreglasses and amosite asbestos in the syrian golden hamster. Part I. Results of a subchronic study and dose selection for a chronic study. *Inhal Toxicol*, 11: 747–784. doi:10.1080/089583799196745 PMID:10477658

Hesterberg TW, Chase G, Axten C *et al.* (1998a). Biopersistence of synthetic vitreous fibres and amosite asbestos in the rat lung following inhalation. *Toxicol Appl Pharmacol*, 151: 262–275. doi:10.1006/taap.1998.8472 PMID:9707503

Hesterberg TW, Hart GA, Chevalier J *et al.* (1998b). The importance of fibre biopersistence and lung dose in determining the chronic inhalation effects of X607, RCF1, and chrysotile asbestos in rats. *Toxicol Appl Pharmacol*, 153: 68–82. doi:10.1006/taap.1998.8522 PMID:9875301

Hesterberg TW, Miiller WC, McConnell EE *et al.* (1993). Chronic inhalation toxicity of size-separated glass fibres in Fischer 344 rats. *Fundam Appl Toxicol*, 20: 464–476. doi:10.1006/faat.1993.1057 PMID:8390950

Hesterberg TW, Miiller WC, Musselman RP *et al.* (1996). Biopersistence of Man-Made Vitreous Fibres and Crocidolite Asbestos in the Rat Lung Following Inhalation. *Fundam Appl Toxicol*, 29: 267–279. doi:10.1006/faat.1996.0031 PMID:8812275

Higashi T, Hori H, Sakurai H *et al.* (1994). Work environment of plants manufacturing asbestos-containing products in Japan. *Ann Occup Hyg*, 38: 489–494, 409. doi:10.1093/annhyg/38.4.489 PMID:7978970

Hill IM, Beswick PH, Donaldson K (1995). Differential release of superoxide anions by macrophages treated with long and short fibre amosite asbestos is a consequence of differential affinity for opsonin. *Occup Environ Med*, 52: 92–96. doi:10.1136/oem.52.2.92 PMID:7757173

Hill RJ, Edwards RE, Carthew P (1990). Early changes in the pleural mesothelium following intrapleural inoculation of the mineral fibre erionite and the subsequent development of mesotheliomas. *J Exp Pathol (Oxford)*, 71: 105–118. PMID:2155636

Hilt B, Langård S, Andersen A, Rosenberg J (1985). Asbestos exposure, smoking habits, and cancer incidence among production and maintenance workers in an electrochemical plant. *Am J Ind Med*, 8: 565–577. doi:10.1002/ajim.4700080608 PMID:3000174

Hobson J, Wright JL, Churg A (1990). Active oxygen species mediate asbestos fibre uptake by tracheal epithelial cells. *FASEB J*, 4: 3135–3139. PMID:2170219

Hodgson JT & Darnton A (2000). The quantitative risks of mesothelioma and lung cancer in relation to asbestos exposure. *Ann Occup Hyg*, 44: 565–601. PMID:11108782

Hodgson JT & Jones RD (1986). Mortality of asbestos workers in England and Wales 1971–81. *Br J Ind Med*, 43: 158–164. PMID:3947577

Homa DM, Garabrant DH, Gillespie BW (1994). A meta-analysis of cancer of the colorectum and asbestos exposure. *Am J Epidemiol*, 139: 1210–1222. PMID:8209879

Howe HL, Wolfgang PE, Burnett WS *et al.* (1989). Cancer incidence following exposure to drinking water with asbestos leachate. *Public Health Rep*, 104: 251–256. PMID:2498974

Hume LA & Rimstidt JD (1992). The biodurability of chrysotile asbestos. *Am Mineral*, 77: 1125–1128.

IARC (1973). Some inorganic and organometallic compounds. *IARC Monogr Eval Carcinog Risk Chem Man*, 2: 1–181.

IARC (1977). Some miscellaneous pharmaceutical substances. *IARC Monogr Eval Carcinog Risk Chem Man*, 13: 1–255. PMID:16821

IARC (1985). Polynuclear aromatic compounds, Part 4, bitumens, coal-tars and derived products, shale-oils and soots. *IARC Monogr Eval Carcinog Risk Chem Hum*, 35: 1–247. PMID:2991123

IARC (1986). Tobacco smoking. *IARC Monogr Eval Carcinog Risk Chem Hum*, 38: 35–394. PMID:3460963

IARC (1987a). Overall evaluations of carcinogenicity: an updating of IARC Monographs volumes 1 to 42. *IARC Monogr Eval Carcinog Risks Hum Suppl*, 7: 1–440. PMID:3482203

IARC (1987b). Silica and some silicates. *IARC Monogr Eval Carcinog Risk Chem Hum*, 42: 1–239. PMID:2824337

IARC (1988). Alcohol Drinking. *IARC Monogr Eval Carcinog Risks Hum*, 44: 1–378. PMID:3236394

IARC (1990). Chromium, nickel and welding. *IARC Monogr Eval Carcinog Risks Hum*, 49: 1–648. PMID:2232124

IARC (1992). Occupational exposures to mists and vapours from strong inorganic acids and other industrial chemicals. *IARC Monogr Eval Carcinog Risks Hum*, 54: 1–310. PMID:1345371

IARC (1993). Beryllium, cadmium, mercury, and exposures in the glass manufacturing industry. *IARC Monogr Eval Carcinog Risks Hum*, 58: 1–415. PMID:8022054

IARC (1997). Silica, Some Silicates, Coal Dust and Para-Aramid Fibrils. *IARC Monogr Eval Carcinog Risks Hum*, 68: 1–475. PMID:9303953

IARC (2000). IARC Working group on the evaluation of carcinogenic risks to humans: ionizing radiation, Part I, X- and gamma- radiation and neutrons. Lyon, France, 26 May-2 June 1999. *IARC Monogr Eval Carcinog Risks Hum*, 75: 1–448. PMID:11203346

IARC (2001). Ionizing radiation, Part 2: some internally deposited radionuclides. *IARC Monogr Eval Carcinog Risks Hum*, 78: 1–559. PMID:11421248

IARC (2002). Man-made vitreous fibres. *IARC Monogr Eval Carcinog Risks Hum*, 81: 1–381. PMID:12458547

IARC (2004). Tobacco smoke and involuntary smoking. *IARC Monogr Eval Carcinog Risks Hum*, 83: 1–1438. PMID:15285078

IARC (2007). Human papillomaviruses. *IARC Monogr Eval Carcinog Risks Hum*, 90: 1–636. PMID:18354839

IARC (2010). Carbon black, titanium dioxide, and talc. *IARC Monogr Eval Carcinog Risks Hum*, 93: 1–452.

IARC (2012c). Biological agents. *IARC Monogr Eval Carcinog Risks Hum*, 100B: PMID:18335640

IARC (2012e). Chemical agents and related occupations. *IARC Monogr Eval Carcinog Risks Hum*, 100F: PMID:18335640

IARC (2012d). Personal habits and household exposures. *IARC Monogr Eval Carcinog Risks Hum*, 100E: PMID:18335640

IARC (2012b). Metals, arsenic, dusts and fibres. *IARC Monogr Eval Carcinog Risks Hum*, 100C: PMID:18335640

IARC (2012a). Radiation. *IARC Monogr Eval Carcinog Risks Hum*, 100D: PMID:18335640

IMA (2005). Industrial Minerals Association-Europe Fact Sheet: Talc, Brussels.

IOM (2006). Asbestos: Selected Cancers. Institute of Medicine of the National Academy of Science [http://books.nap.edu/catalog/11665.html]

Jakobsson K, Albin M, Hagmar L (1994). Asbestos, cement, and cancer in the right part of the colon. *Occup Environ Med*, 51: 95–101. doi:10.1136/oem.51.2.95 PMID:8111470

Jansson C, Johansson AL, Bergdahl IA *et al.* (2005). Occupational exposures and risk of esophageal and gastric cardia cancers among male Swedish construction workers. *Cancer Causes Control*, 16: 755–764. doi:10.1007/s10552-005-1723-2 PMID:16049815

Jaurand MC (1996). Use of in-vitro genotoxicity and cell transformation assays to evaluate the potential carcinogenicity of fibres. *IARC Sci Publ*, 55–72. PMID:9101317

Jehan N (1984) *Sustainable management of mineral resources with special reference to asbestos and silica in northern Pakistan.* Ph.D., National Centre of Excellence in Geology, University of Peshawar.

Kamp DW & Weitzman SA (1999). The molecular basis of asbestos induced lung injury. *Thorax*, 54: 638–652. doi:10.1136/thx.54.7.638 PMID:10377212

Kane AB (2006). Animal models of malignant mesothelioma. *Inhal Toxicol*, 18: 1001–1004. doi:10.1080/08958370600835393 PMID:16920675

Kang SK, Burnett CA, Freund E *et al.* (1997). Gastrointestinal cancer mortality of workers in occupations with high asbestos exposures. *Am J Ind Med*, 31: 713–718. doi:10.1002/(SICI)1097-0274(199706)31:6<713::AID-AJIM7>3.0.CO;2-R PMID:9131226

Karjalainen A, Pukkala E, Kauppinen T, Partanen T (1999). Incidence of cancer among Finnish patients with asbestos-related pulmonary or pleural fibrosis. *Cancer Causes Control*, 10: 51–57. doi:10.1023/A:1008845332422 PMID:10334642

Kauppinen T & Korhonen K (1987). Exposure to asbestos during brake maintenance of automotive vehicles by different methods. *Am Ind Hyg Assoc J*, 48: 499–504. PMID:3591672

Kimura K (1987). [Asbestos and environment.]*Dig Sci Lab*, 42: 4–13.

Kjærheim K, Ulvestad B, Martinsen JI, Andersen A (2005). Cancer of the gastrointestinal tract and exposure to asbestos in drinking water among lighthouse keepers (Norway). *Cancer Causes Control*, 16: 593–598. doi:10.1007/s10552-004-7844-1 PMID:15986115

Kleymenova EV, Horesovsky G, Pylev LN, Everitt J (1999). Mesotheliomas induced in rats by the fibrous mineral erionite are independent from p53 alterations. *Cancer Lett*, 147: 55–61. doi:10.1016/S0304-3835(99)00275-X PMID:10660089

Kogan FM, Vanchugova NN, Frasch VN (1987). Possibility of inducing glandular cancer of the stomach in rats exposed to asbestos. *Br J Ind Med*, 44: 682–686. PMID:3676121

Kratzke RA, Gazdar AF (2005). *Oncogenes and tumor suppressor genes in malignant mesothelioma.* In: *Malignant Mesothelioma: Advances in Pathogenesis, Diagnosis and Translational Therapies.* Pass HI, Vogelzang NJ Carbone M, editors. New York: Springer Science & Business Media, Inc., pp. 124-141.

Krstev S, Dosemeci M, Lissowska J *et al.* (2005). Occupation and risk of cancer of the stomach in Poland. *Occup Environ Med*, 62: 318–324. doi:10.1136/oem.2004.015883 PMID:15837853

Landrigan PJ, Lioy PJ, Thurston G *et al.*NIEHS World Trade Center Working Group (2004). Health and environmental consequences of the world trade center disaster. *Environ Health Perspect*, 112: 731–739. PMID:15121517

Langer AM & Nolan RP (1994). Chrysotile: its occurrence and properties as variables controlling biological effects. *Ann Occup Hyg*, 38: 427–51. . PMID:7978965

Langseth H, Johansen BV, Nesland JM, Kjaerheim K (2007). Asbestos fibres in ovarian tissue from Norwegian pulp and paper workers. *Int J Gynecol Cancer*, 17: 44–49. doi:10.1111/j.1525-1438.2006.00768.x PMID:17291230

Langseth H & Kjærheim K (2004). Ovarian cancer and occupational exposure among pulp and paper employees in Norway. *Scand J Work Environ Health*, 30: 356–361. PMID:15529799

Lash TL, Crouch EA, Green LC (1997). A meta-analysis of the relation between cumulative exposure to asbestos and relative risk of lung cancer. *Occup Environ Med*, 54: 254–263. doi:10.1136/oem.54.4.254 PMID:9166131

Le Bouffant L, Daniel H, Henin JP *et al.* (1987). Experimental study on long-term effects of inhaled MMMF on the lungs of rats. *Ann Occup Hyg*, 31: 4B765–790. doi:10.1093/annhyg/31.4B.765 PMID:3450235

Lee KP, Barras CE, Griffith FD *et al.* (1981). Comparative pulmonary responses to inhaled inorganic fibres with asbestos and fibreglass. *Environ Res*, 24: 167–191. doi:10.1016/0013-9351(81)90143-2 PMID:6260477

Lee KP, Reinhardt CF (1984). *Biological studies on inorganic potassium titanate fibres.* In: *Biological Effects Man-Made Mineral Fibres:Proceedings of a WHO/IARC Conference in Association with JEMRB and TIMA.* Copenhagen: World Health Organization, Regional Office for Europe, 323–333.

Levy BS, Sigurdson E, Mandel J *et al.* (1976). Investigating possible effects of abestos in city water: surveillance of gastrointestinal cancer incidence in Duluth, Minnesota. *Am J Epidemiol*, 103: 362–368. PMID:1258862

Liddell FD, McDonald AD, McDonald JC (1997). The 1891–1920 birth cohort of Quebec chrysotile miners and millers: development from 1904 and mortality to 1992. *Ann Occup Hyg*, 41: 13–36. PMID:9072947

Lindor NM, Lindor CY, Greene MH (2006). *Hereditary neoplastic syndromes.* In: *Cancer Epidemiology and Prevention,* 3rd ed. Schottenfeld D, Fraumeni JF, Jr., editors. New York: Oxford University Press, pp. 562-576.

Lippmann M (1990). Effects of fibre characteristics on lung deposition, retention, and disease. *Environ Health Perspect*, 88: 311–317. doi:10.2307/3431093 PMID:2272328

Lippmann M, Yeates DB, Albert RE (1980). Deposition, retention, and clearance of inhaled particles. *Br J Ind Med*, 37: 337–362. PMID:7004477

Loomis D, Dement JM, Richardson D, Wolf S (2009). Asbestos fibre dimensions and lung cancer mortality among workers exposed to chrysotile. *Occup Environ Med*, 67: 580–584. doi:10.1136/oem.2008.044362 PMID:19897464

López-Ríos F, Chuai S, Flores R *et al.* (2006). Global gene expression profiling of pleural mesotheliomas: overexpression of aurora kinases and P16/CDKN2A deletion as prognostic factors and critical evaluation of microarray-based prognostic prediction. *Cancer Res*, 66: 2970–2979. doi:10.1158/0008-5472.CAN-05-3907 PMID:16540645

Lu J, Keane MJ, Ong T, Wallace WE (1994). In vitro genotoxicity studies of chrysotile asbestos fibres dispersed in simulated pulmonary surfactant. *Mutat Res*, 320: 253–259. doi:10.1016/0165-1218(94)90078-7 PMID:7508551

Luce D, Bugel I, Goldberg P *et al.* (2000). Environmental exposure to tremolite and respiratory cancer in New Caledonia: a case–control study. *Am J Epidemiol*, 151: 259–265. PMID:10670550

Lund LG, Williams MG, Dodson RF, Aust AE (1994). Iron associated with asbestos bodies is responsible for the formation of single strand breaks in phi X174 RFI DNA. *Occup Environ Med*, 51: 200–204. doi:10.1136/oem.51.3.200 PMID:8130850

Lynch KM & Smith WA (1935). Pulmonary asbestosis III: Carcinoma of the lung in asbeto-silicosis. *Am J Cancer*, 24: 56–64.

Madl AK, Clark K, Paustenbach DJ (2007). Exposure to airborne asbestos during removal and installation of gaskets and packings: a review of published and unpublished studies. *J Toxicol Environ Health, Part B*, 10: 259–286.

Magnani C, Agudo A, González CA *et al.* (2000). Multicentric study on malignant pleural mesothelioma and non-occupational exposure to asbestos. *Br J Cancer*, 83: 104–111. PMID:10883677

Magnani C, Dalmasso P, Biggeri A *et al.* (2001). Increased risk of malignant mesothelioma of the pleura after residential or domestic exposure to asbestos: a case–control study in Casale Monferrato, Italy. *Environ Health Perspect*, 109: 915–919. doi:10.2307/3454992 PMID:11673120

Magnani C, Ferrante D, Barone-Adesi F *et al.* (2008). Cancer risk after cessation of asbestos exposure: a cohort study of Italian asbestos cement workers. *Occup Environ Med*, 65: 164–170. doi:10.1136/oem.2007.032847 PMID:17704197

Maltoni C, Minardi F (1989). *Recent results of carcinogenicity bioassays of fibres and other particulate materials.* In: *Non-occupational Exposure to Mineral Fibres.* IARC Scientific Publ. Vol. 90. Bignon J, Peto J Saracci R, editors. Lyon: International Agency for Research on Cancer, pp. 46–53.

Manning CB, Vallyathan V, Mossman BT (2002). Diseases caused by asbestos: mechanisms of injury and disease